First Time in Full Color

25

Golwalla's MEDICINE *for Students*

A Reference Book *for* The Family Physician

Aspi F Golwalla
Sharukh A Golwalla

Edited by
Milind Y Nadkar

JAYPEE

Golwalla's
MEDICINE for Students

Golwalla's MEDICINE for Students

A Reference Book for the Family Physician

Twenty-Fifth Edition

ASPI F GOLWALLA MD FACC FCPS FCCP
Emeritus Professor of Medicine
Seth GS Medical College and KEM Hospital
Mumbai, Maharashtra, India

SHARUKH A GOLWALLA MD (Med) DM (Card) FCCP
Visiting Cardiologist
Breach Candy Hospital, Jaslok Hospital and HN Reliance Hospital
Mumbai, Maharashtra, India

Edited by

MILIND Y NADKAR MD FICP FACP
Professor of Medicine & Chief of Rheumatology & Emergency Medicine
Seth GS Medical College and KEM Hospital
Mumbai, Maharashtra, India

The Health Sciences Publisher
New Delhi | London | Panama

Jaypee Brothers Medical Publishers (P) Ltd

Headquarters
Jaypee Brothers Medical Publishers (P) Ltd.
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
Fax: +91-11-43574314
E-mail: jaypee@jaypeebrothers.com

Overseas Offices
J.P. Medical Ltd.
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-20 3170 8910
Fax: +44(0)20 3008 6180
E-mail: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld. 235, 2nd Floor, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
E-mail: cservice@jphmedical.com

Jaypee Brothers Medical Publishers (P) Ltd.
17/1-B, Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
E-mail: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
Bhotahity, Kathmandu, Nepal
Phone: +977-9741283608
E-mail: kathmandu@jaypeebrothers.com

Website: www.jaypeebrothers.com
Website: www.jaypeedigital.com

Golwalla's Medicine for Students

Twenty-Fourth Edition: 2014

Twenty-Fifth Edition: **2017**

ISBN: 978-93-5152-474-8

PREFACE

The purpose and scope of this widely read book at times referred to as a Bible in Medicine remains the same when it was first published in the year 1952 namely to help the undergraduate medical students with necessary information presented on easily imbibable form for the final MBBS examination both for Theory and Viva.

Over the years, the book has spread its wings. To add to this its aim is the acceptance by the students of Homeopathy, Dentistry, Physiotherapy and even Ayurveda, where the question papers in the subject of Medicine have found wide approval.

The original author of the book has been aging but the younger author is aware that new vigour and fresh ideas are needed to ensure that every aspect in the test is kept up-to-date.

The authors welcome the Editor, a pupil of the senior author in yesteryears and now a distinguished head of the leading monthly journal in the country and other literary achievements as a collaborator in this revised edition, and also for such future revisions that will be called for.

Illustrations have been used freely whenever it was thought they would be purposeful in pathogenesis and diagnosis of diseases. There are more number of tables and figures introduced in this edition.

There might be room for improvement in some aspects, notwithstanding the amount of time and labour bestowed upon it.

Criticisms and suggestions are invited and will be received with gratitude by the authors and Editor.

Date of Publication
December 2016

Aspi F Golwalla
Sharukh A Golwalla

Edited by
Milind Y Nadkar

CONTENTS

CHAPTER 1

Gastroenterology

1. INVESTIGATIONS OF GASTROINTESTINAL DISEASE

STOOL EXAMINATION

Naked eye—Consistency, presence of blood, mucus, helminths. Occult blood if positive suggests – GI bleeding, growth, tuberculous lesion or inflammatory bowel disease. Some patients on aspirin, mesenteric vascular disease, vegetative forms and cysts of *E. histolytica*.

Microscopic—For RBCs, pus cells in bacillary dysentery and inflammatory bowel disease. Presence of ova of *Ascaris* or *Ankylostoma*.

Stool culture in selected cases of chronic infective diarrhoea and pseudomembranous colitis.

HEMATOLOGICAL AND BIOCHEMICAL TESTS

RBC count, Hb, MCV, blood film, serum iron, iron binding capacity, red cell folate, serum B_{12}, serum albumin, serum electrolytes.

GASTRIC ACID SECRETIONS

Are usually not measured, but sometimes provide useful corroborative information. In normal people, basal acid output is about 2–4 mmol/hour rising to about 10–30 mmol/hour in the hour after s.c. injection of Pentagastrin 6 mcg/kg. Pentagastrin not available nowadays (An endoscopic method for measuring gastric acid output has been developed but requires further validation). Gastric acid measurements are of diagnostic value:

(i) When a gastrinoma is suspected.
(ii) An ulcer has recurred after surgery.
(iii) To detect achlorhydria in case of gastric ulcer. Occurrence of gastric ulcer in presence of achlorhydria is indicative of malignancy since most cases of benign gastric ulcer have some acid secretion.

FASTING SERUM GASTRIN LEVELS: *INDICATIONS*

Multiple ulcers or ulcers in unusual locations associated with severe oesophagitis, resistant to therapy, preoperative family history of peptic ulcer disease, postoperative ulcer recurrence, basal hyperchlorhydria, unexplained diarrhoea or steatorrhoea, hypercalcaemia, prominent gastric or duodenal folds.

RADIOLOGY

Plain films of abdomen. Supine and erect films are taken for diagnosis of any acute abdominal condition especially obstruction or perforation. It can also reveal changes in soft tissues produced by masses or inflammation, pneumoperitoneum, gallstones, calcification of gallbladder wall, liver calcification, urinary calculi, appendoliths.

Chest radiographs can reveal a small pneumoperitoneum, level of the diaphragm, intrathoracic conditions, e.g. pneumonia.

BARIUM STUDIES

With advances in endoscopy, the role of barium studies has now become restricted to barium swallow for the oesophagus and small bowel enema/enteroclysis for the jejunum and ileum. Now the CT scan has also become an important modality for small bowel pathology, especially with the use of CT enteroclysis (Fig. 1). Table 1 enumerates various conditions that can be diagnosed on barium studies.

ENDOSCOPY

Diagnostic indications for endoscopy are listed in Table 2.

Colonoscopy is gold standard for diagnosis of colonic mucosal disease.

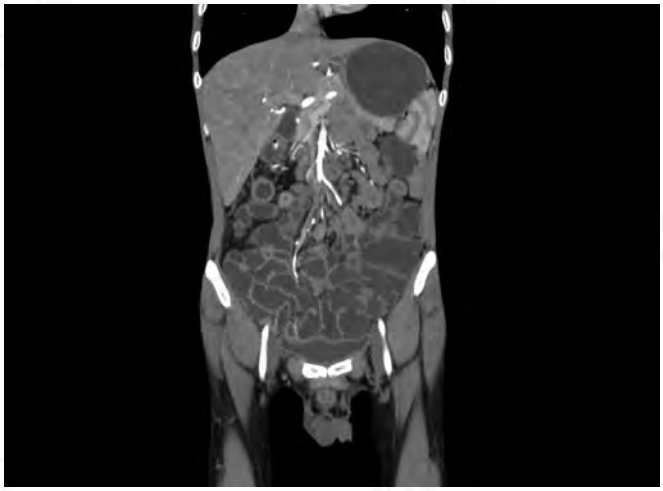


Fig. 1: Enteroclysis CT abdomen

Contraindications for colonoscopy—Perforated intestine, acute diverticulitis, deep ulcerations, severe ischemic necrosis, fulminant colitis, severe cardiac or pulmonary diseases.

Capsule endoscopy. CE is performed by ingestion of a small, disposable battery powered pill containing a metal oxide semi-conductor camera. Four light emitting diodes illuminate the lumen of the bowel.

Indications—1. Obscure GI bleeding. 2. Small bowel Crohn's disease. 3. Diagnosis of coeliac disease and its complications. 4. Screening for polyps for small bowel polyposis syndromes and small bowel tumours. 5. NSAIDs enteropathies.

Contraindications—1. Patients with known or suspected obstruction, strictures, fistulas. 2. Patients with cardiac pacemaker or other implanted electromedical devices. 3. Patients with swallowing disorders. 4. Pregnancy.

Endosonography

USG of GI tract

USG is an important modality in abdominal imaging.

Indications. 1.Congenital—Hypertrophicpyloricstenosis, malrotation. 2. Acute bowel pathology—Appendicitis, obstruction, intussusception, colitis, sigmoid diverticulitis. 3. Tumours. 4. Miscellaneous—Ileocaecal tuberculosis, duodenal ulcer, round worms.

Endoscopic Ultrasonography

With EUS, lesions located in the gut wall as well as those immediately outside it can be well seen. Endoscopic ultrasonography is useful in diagnosis of submucosal tumours and in assessing the infiltration and depth of malignancy of GI tract, and also in detection of metastasis in nearby lymph nodes.

Indications—Cancer of oesophagus, mediastinal masses, submucosal tumours, bile duct stones, pancreatic tumours, pancreatic pseudocysts, gallbladder microlithiasis, ampullary growths. Colorectal stenting.

Contraindications for colonoscopy—Perforated intestine, acute diverticulitis, deep ulcerations, severe ischemic necrosis and fulminant colitis, severe cardiac or pulmonary diseases.

Table 1: Conditions diagnosed on barium studies

Barium swallow
Oesophageal filling defects
Strictures (sensitivity greater than that of endoscopy)
Gastro-oesophageal reflux
Oesophageal varices
Achalasia
Scleroderma
Oesophageal webs
Candidiasis
Barium meal
Peptic ulcer
Gastric ulcer
Outlet obstruction
Disorders of gastric emptying
Barium meal with follow-through
Abdominal pain
Persistent GI bleed
Malabsorption
Partial bowel obstruction
Crohn's disease
Small bowel enema
Same as barium follow-through
Barium enema (Double-contrast)
Narrowing of lumen
Strictures (colonic diverticulitis, Crohn's disease)
Dilatation of lumen
Obstruction, volvulus, paralytic ileus,
ulcerative colitis, megacolon, Hirschsprung's disease.
Miscellaneous
Filling defects
Ulceration
Diverticular disease
Displacement of colon (Hepatosplenomegaly, pelvic tumours)

Table 2: Diagnostic indications for endoscopy

Upper GI endoscopy		
Oesophageal	Hiatal hernia	Cancer (Figs. 2A and B)
	Reflux oesophagitis	Barrett's oesophagus
	Strictures	Oesophagitis
	Webs	Varices
	Cancer	Mallory-Weiss syndrome
	Corrosive ingestion (Fig. 3)	
Stomach	Gastritis	Polyp
	Ulcers (including biopsy for *H. pylori*)	Menetrier's disease
	Tumours	
	Infiltration (Lymphoma)	
Duodenum	Duodenitis	Tumours
	Ulcer	Polyps
Miscellaneous	Dyspepsia	Upper GI bleed
	Gastric outlet obstruction	Post-op. stomach
Lower GI endoscopy		
Colonoscopy	Radiological abnormality anastomosis	Inspection of colon
Lower GI bleed	Follow up of polyp or cancer	Some cases of colitis
(Barium enema does not adequately visualise this area).		
Proctoscopy—For examination of middle and lower parts of anal canal, e.g. haemorrhoids, fissures, carcinoma of anorectal region.		
Sigmoidoscopy—To evaluate rectum or sigmoid colon before anorectal surgery or in a patient in whom barium enema is indicated. (*Primarily used for evaluation of diarrhoea and rectal outlet bleeding*)		

MUCOSAL BIOPSY

Mucosal biopsies can be obtained under direct vision with endoscope (oesophagus, stomach, duodenum, rectum, colon). Small intestinal biopsy can be obtained with pinch biopsy forceps. Normal histology with a well-formed villous pattern almost excludes diffuse small intestinal mucosal disease. In difficult cases, jejunal biopsy with a suction (e.g. Crosby) capsule may provide further information, and allows examination of dissecting microscopic appearances.

GI MOTILITY

Oesophageal Motility

Barium swallow with video fluoroscopy:

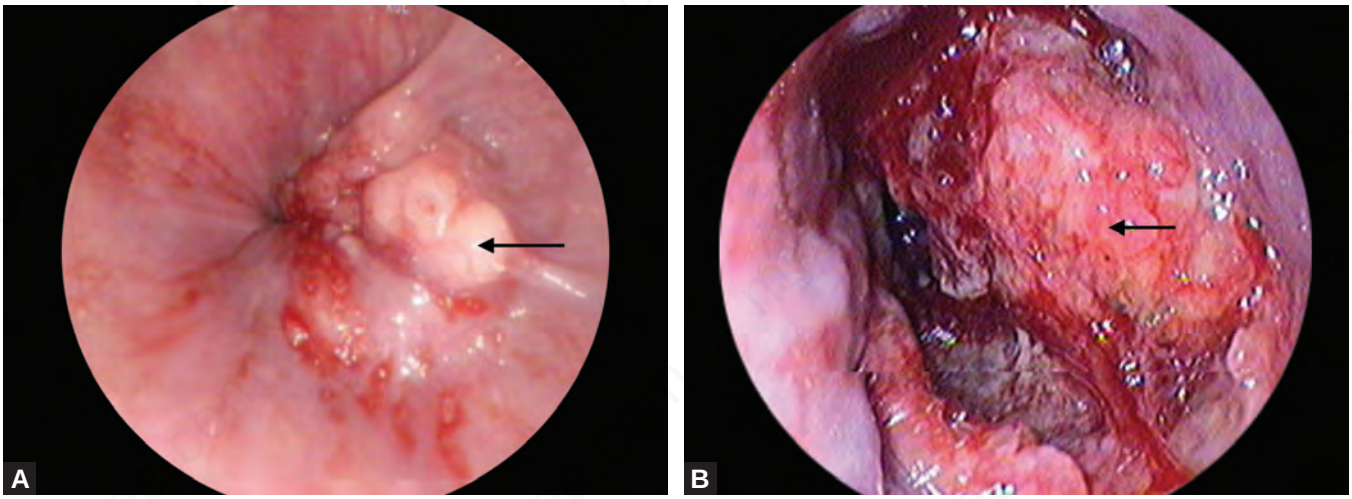
Upper oesophageal sphincter disorders
Body motility
Non-propulsive (tertiary contractions)
Uncoordinated or weak post-swallow contractions

Manometry:

Upper oesophageal sphincter—Tone of the sphincter and relaxation during swallowing.

Lower oesophageal sphincter tonic pressure and relaxation.

Gastric emptying—Amount of radioisotope retained in the stomach against time, carried out following a test meal containing labelled solids and liquids with different isotopes.



Figs. 2A and B: Carcinoma of oesophagus

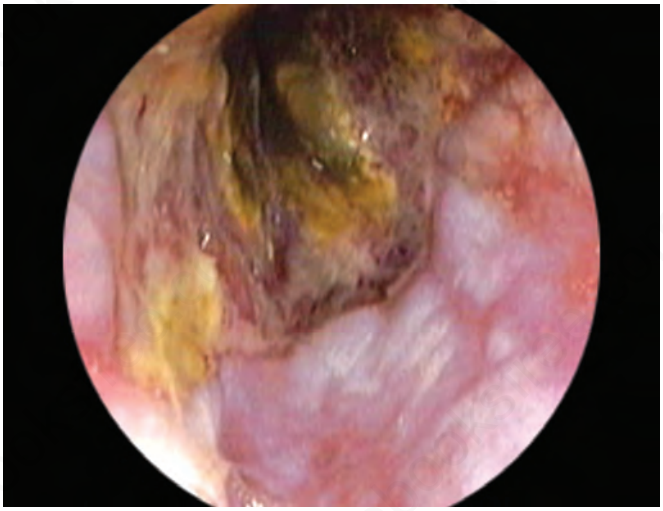


Fig 3: Oesophagitis due to corrosive ingestion

Small Intestinal Transit

Barium follow-through—Noting the time taken for contrast to reach terminal ileum (normal about 90 minutes)

Lactulose-hydrogen breath test—Measuring serial breath hydrogen samples following ingestion of a non-absorbable carbohydrate. Rise in breath hydrogen concentration suggests arrival of poorly digested carbohydrate due to fermentation by colonic bacteria.

Colonic transit. Plain radiograph of abdomen on day 5 after ingestion of different shapes of inert pellets on days 1–3. The test is useful in evaluation of chronic constipation due to slow transit.

RADIOISOTOPE TESTS

Radionuclide imaging becomes necessary when barium studies and endoscopy are not conclusive.

- *Gastric emptying time*—for gastroparesis
- *Urea breath test* for diagnosis of *H. pylori*
- *Meckel's scan* for diagnosis of Meckel's diverticulum
- *Labelled red cell scan* for recurrent or obscure GI bleeding.
- *Labelled leucocyte scan* for localised abscess collections in inflammatory bowel disease.
- *SeHCAT scan* for diagnosis of diarrhoea (bile acid-related)
- *Triolein scan* for diagnosis of malabsorption
- *Epithelial permeability test* for investigation of protein-losing enteropathy.

ANGIOGRAPHY

Transfemoral triple vessel angiography (coeliac axis, superior and inferior mesenteric arteries) is used when the site of bleeding cannot be determined by endoscopy. Endoscopic ultrasonography is useful in diagnosis of submucosal tumours and in assessing the infiltration and depth of malignancy of GI tract, and also in detection of metastasis in nearby lymph nodes.

SCANNING METHODS AND THEIR USES

Ultrasound

- Abdominal masses (cysts, tumours, abscess, hepato/splenomegaly)
- Ascites
- Depth of invasion of tumours (endoluminal endoscopic scan)
- Aspiration biopsy

CT Scan

- Bowel wall thickening
- Large colonic carcinoma
- Depth of invasion of tumours

2. THE TONGUE IN DIAGNOSIS

CONGENITAL LINGUAL DISORDERS

Apart from developmental anomalies such as tongue tie, following variations are without clinical significance:

1. *Fissured tongue* (Scrotal tongue)—Deep fissures mostly in longitudinal direction.
2. *Geographical tongue* (Benign migratory glossitis or the wandering rash of the tongue)—For no apparent reason the filiform papillae disappear in oval patches and leave smooth red areas which look like the boundaries of countries on a map.
3. *Median rhomboid glossitis*—Rhomboidal or oval, red, slightly elevated area on the dorsum of the tongue due to failure of fusion of lateral segments of the tongue. (It may be a chronic hypoplastic candidiasis rather than a developmental anomaly).
4. *Furred tongue*—Fur is formed continuously and normally removed by food and saliva. Fur is quite marked if the tongue is not used much, and in smokers.

5. *Rough clean tongue*—Rather large tongue with unusually well-marked fungiform papillae.
6. *Horny tongue* (Crocodile or toad tongue)—Various types of cornification of the mucosa.

Size

Macroglossia

Acute—(i) Inflammatory. (ii) Non-inflammatory in angioedema.

Chronic—Acromegaly, myxoedema, Down's syndrome, cretinism, amyloid disease or Von Gierke's glycogen storage disease. Other rare causes are congenital arteriovenous fistula between lingual artery and vein, pachydermoperiostosis, and lymphangioma circumscripta superficialis due to hyperplasia of lymphatic vessels.

Microglossia

Dehydration, atrophic glossitis, wasting due to hypoglossal nerve involvement, facial hemiatrophy, or pseudobulbar palsy (small pointed compact looking tongue). In myasthenia gravis atrophy of the tongue may give rise to triple longitudinal furrowing. Bilateral atrophy (with fasciculations) in progressive bulbar paralysis.

ULCERS

1. *Traumatic*—(a) At margins of tongue in epilepsy. (b) Ulcer of frenum (sublingual ulcer) in whooping cough. (c) Dental—opposite a carious tooth.
2. *Tuberculous ulcer*—associated with pulmonary tuberculosis. It is painful and tends to occur near the tip of the tongue.
3. *Recurrent aphthous ulcers*—of unknown aetiology, or at times with idiopathic steatorrhoea or ulcerative colitis. Rarely from Stevens-Johnson syndrome (erythema multiforme) and Behcet's syndrome (recurrent oral, genital and eye ulceration with neurological signs).
4. *Epitheliomatous ulcer*—deep and indurated.
5. *Syphilis*—(a) Primary: Indurated painless ulcer, lymphadenopathy. (b) Secondary: 'Snail track' ulcers with greyish slough or mucus patches and lymphadenopathy. (c) Tertiary: Often midline, punched out ulcers.
6. *Hand, foot and mouth disease*—Round or ovoid ulcers anywhere on mucosa (with vesicular rash on extremities).

COLOUR

1. Pale tongue in anemia. Blotting paper-like pallor with pigmented margins in Ankylostoma infection at times.
2. Red raw, 'angry looking' tongue in sprue, pellagra, severe and untreated diabetes, prolonged febrile illness.
3. White tongue

   Lichen planus—Multiple white plaque-like areas.

   White patches or flakes on tongue due to curdled milk, thrush, syphilitic patches.

   Leukoplakia denotes any persistent white patch on mucous membrane of dorsum of tongue (or lips, gums or cheek). It is mostly seen in men over 40. Predisposing factors: Local include smoking, betel nut chewing, spicy food and syphilis. Leukoplakia is a precancerous lesion. Systemic: Candidiasis, lichen ruber mucosae, SLE, papilloma, chronic kidney failure.

   Hairy leukoplakia almost exclusively occurs in patients with HIV disease. It is characterised by white, non-removable lesions particularly affecting the lateral margins and ventral aspects of the tongue. The white patches can also have a homogenous plaque like appearance. At times hairy leukoplakia can be observed in a small number of non-HIV infected immunocompromised individuals.
4. Magenta colour—in riboflavin deficiency.
5. Blue tongue—denotes central cyanosis.
6. Purple tongue in polycythemia.
7. Dark red or bluish red tongue—in polycythemia vera, riboflavin deficiency, broad spectrum antibiotics.
8. Strawberry tongue—Red tongue with the papillae standing out as white dots in scarlet fever, Kawasaki's disease and toxic shock syndrome.
9. Raspberry tongue—In early stages of scarlet fever, the tongue shows scattered red dots on a grey background. It is due to red fungiform papillae sparsely dotted over the grey tongue.
10. Excessively furred tongue—(a) In all febrile conditions especially typhoid. (b) Poor oral hygiene and mouth breathing. (c) Trismus as from a carious tooth.
11. Yellow tongue—Rarely in jaundice, or due to irritants like nitric or hydrochloric acid.
12. Black tongue—Due to fungus infection, iron, bismuth, opium or tobacco.
13. Slate-blue tongue—in hemochromatosis.
14. Oral hairy tongue—Yellowish brown or black furry patches made up of hypertrophied and densely matted papillae usually from antibiotic ingestion or excessive smoking. Oral hairy tongue should be differentiated from oral hairy leukoplakia which is a white lesion caused by EB virus.

15. Brownish fur with dry tongue (Parrot tongue)—in chronic kidney failure.
16. Small red lesions in hereditary telangiectasia.

MOISTURE

The tongue in health is moist. Dryness of the tongue may be part of general dehydration as in diarrhoea, vomiting and diabetes mellitus. It is worsened by mouth breathing. Certain atropine-like drugs may cause appearance of dry tongue and mouth. Bone-dry tongue in Sjögren's syndrome.

PIGMENTATION

1. *Congenital*—Naevi, Peutz-Jeghers syndrome (circumoral and intraoral melanosis with intestinal polyposis), racial. 2. *Acquired*—(a) Malabsorption or chronic cachexia. (b) Drugs—ACTH, phenothiazines, amodiaquine. (c) Endocrine—Addison's disease, ACTH producing tumours, Albright's syndrome, polyostotic fibrous dysplasia, Nelson's syndrome (hyperpituitarism following adrenalectomy). (d) Dental amalgam. (e) Neoplastic—melanoma, acanthosis nigricans.

SURFACE

1. *Smooth or bald tongue* (atrophic glossitis)—Atrophy of papillae resulting in glossy or varnished tongue may be due to iron deficiency anemia, pernicious anemia, B complex deficiency or malabsorption.
2. *Fissured tongue*—Vitamin B complex deficiency, Mongolian idiocy, acromegaly, acute glossitis, dental trauma, senility or bad oral hygiene, congenital scrotal tongue.
3. *Scarred tongue*—Scars on the tongue may be traumatic, secondary to ulcers from 'tongue-biting' as in epilepsy.
4. *Mushroom-like tongue*—Sore tongue covered with whitish slough in acid poisoning.

MOVEMENTS

1. *Tremors*—(a) Slow rhythmic tremor stopping on voluntary extrusion of tongue in Parkinsonism. (b) Backward and forward 'trombone' tremor of GPI. (c) Miscellaneous causes—multiple sclerosis, prolonged fevers, wasting diseases, senility, chronic alcoholism and excessive smoking and thyrotoxicosis.
2. *Lizard tongue* (Jack-in-the-box or wormian tongue) in rheumatic chorea. After protrusion, the tongue is shot back into the mouth.
3. *Deviated tongue* with tip and median raphe curving round towards the affected side in hypoglossal nerve paralysis. Also in malignant infiltration, scarification after burns or severe ulceration, facial paralysis.
4. *Immobile tongue* (Paretic tongue)—Bilateral lingual paralysis, advanced malignancy of tongue, bulbar palsy, syringomyelia. Sluggish and slow protrusion in mental retardation. Increasingly slow movements in myasthenia gravis.
5. *Rolling movements*—in cretins, Mongols and frontal lobe tumours. In case of Mongols, cretins and in macroglossia, a part of the tongue remains permanently protruded outside the mouth.
6. *Chewing tongue*—Movements of the tongue as in act of chewing in athetosis.
7. *Myotonic reaction*—After a sharp tap on the protruded tongue in myotonia atrophica.
8. *Spasm of the tongue* may be tonic with the tongue becoming small, rigid, conical as in anxiety and general debility, or clonic (the tongue displaying sudden jerks) as in chorea, epilepsy, habit spasm, multiple sclerosis, GPI, hysteria and stuttering.

MISCELLANEOUS DISORDERS

Amyloid tongue—Enlarged tongue with mottling of dark purple areas with translucent matter as part of generalised amyloidosis.

Purpuric spots on the tongue may appear in senile purpura.

Painful tongue—Paroxysms of agonising pain in glossopharyngeal neuralgia.

Alligator tongue—Dry, thick, furrowed and irregular tongue in diabetes mellitus.

Cotton wool patches on dorsum of tongue may be seen in xerostomia in graft-versus-host disease. These are areas of amorphous keratinization as seen in lichen planus.

Truncated tongue—Rarely a tuberculous ulcer at tip of tongue with oedema of the rest of the tongue may impart a truncated, amputated look to the tongue.

Frenulated tongue in Oro-facial-digital syndrome.

Fatiguability of tongue—In myasthenia gravis weakness of muscles of the tongue leads to difficulty in articulation.

Caviar lesions—Varicosities of sublingual veins may be seen on under surface of the tongue in elderly individuals, as also in mediastinal obstruction.

Secondary deposits—Small, yellowish grey nodules rarely in medullary carcinoma of thyroid.

3. STOMATITIS AND ORAL ULCERATION

Causes of stomatitis and oral ulcerations are listed in Table 3.

4. DYSPHAGIA

Dysphagia indicates a delay in the passage of solids or liquids from the mouth to the stomach. Dysphagia should be

Table 3: Causes of stomatitis and oral ulcerations

Stomatitis	*Causes*	*Clinical features*	*Treatment*
Catarrhal	Local: Excessive tobacco, alcohol, spices, antibiotics, drugs (gold, iodide) Systemic: Debility, infectious disease	Red mucous membrane with increased exudate	Elimination of cause. Hexidine or iodine mouth wash. Vit. B complex
Recurrent aphthous stomatitis (RAS)	Possible etiological factors: Positive family history in 1/3. Stress, local trauma, food allergy, in association with menstrual cycles. Episodic mouth ulcers in cyclic neutropenia and HIV infection. Also Behcet's disease, and Sweet's syndrome, Coeliac disease.	Tiny shallow ulcers on erythematous base covered with a greyish white exudate	Systemic: Oral steroids Topical: Mouth washes: Sodium chlorid. Compound thymol glycerin. Antiseptics: Chlorhexidine 0.2%. Povidone iodine 1%. Kamillosan-N mouth spray t.d.s. before meals. Tooth brushing with hydrogen peroxide sodium bicarbonate paste. Immunomodulators: Tetracycline 250 mg capsule in 10 ml water. Swirl then spit qds Triamcinolone acetonide 0.1% Paste qds. Betamethasone 500 µg soluble tabs. swirl and swallow b.d. Beclomethasone dipropionate 100 µg. aerosol sprayed directly qds.
Infection Bacterial (Vincent's angina)	Predisposing factors—pre-existing gingivitis or local trauma, tobacco use	Ulcer surface covered by a grey pseudomembranous slough demarcated from surrounding mucosa by linear erythema. Increased salivation, foetid odour, spontaneous gingival bleeding, lymphadenopathy and fever.	Metronidazole 200 mg tds for 3 days. After control of acute phase, oral hygiene and surgical correction of distorted gingivae.
Viral	Herpes simplex	Common in children. Severe ulceration of oral mucous membrane with fever, malaise and lymphadenopathy. Initial formation of discrete, spherical grey vesicles which rupture after few hours to form ulcers. Course 2–3 weeks.	Bed rest. Mouth washes. In severe cases acyclovir
	Herpes-varicella zoster	Painful oral ulcer. Tear drop rash of chickenpox.	Symptomatic treatment
	Infectious mononucleosis	Ulcers particularly on fauces.	Symptomatic treatment
	Hand, foot and mouth disease	Round or oval ulcers anywhere on buccal mucosa with rash on extremities.	Symptomatic treatment
Fungal	Thrush (Pseudomembranous candidiasis) Occurs in infants, debilitated adults such as heroin addicts, elderly and after antibiotic and steroid therapy. Early feature of AIDS.	White slightly raised patches resembling milk curds, easily removed leaving a raw bleeding surface.	Ketoconazole 200 mg (for children under 12, 1/4 dose). In infants 0.5% gentian violet applied tds.

Contd...

Contd...

Stomatitis	*Causes*	*Clinical features*	*Treatment*
Spirochaetal	Secondary syphilis	Circular, mucous patches, often greyish white with red areola	Treatment of syphilis
Drug-induced	Hypersensitivity, cytotoxic drugs (e.g. Methotrexate)	Stomatitis and ulceration of buccal, labial and palatal mucosa.	Symptomatic treatment
Vitamin deficiency	Nicotinic acid deficiency	Raw red tongue in pellagra	Vitamin B complex
GI disorders	Crohn's disease Coeliac disease		
Blood disorders	Acute leukaemia or neutropenia		
Dermatological	Erythema multiforme and Stevens-Johnson syndrome, Lichen planus, Pemphigoid, SLE	See appropriate section	
Systemic disease Neoplasia	Behcet's syndrome, HIV Carcinoma Kaposi's sarcoma		

distinguished from odynophagia which is discomfort or pain on swallowing hot or cold liquids, and occasionally alcohol. In general, mechanical causes lead to dysphagia for solid foods, whereas patients with motility disorders tend to complain of non-progressive dysphagia for both liquids and solids from the onset.

CAUSES OF DYSPHAGIA

Causes of dysphagia are enumerated in Table 4.

Investigation of a case of Dysphagia

HISTORY

I. Age and sex—*Children* – Cleft palate, foreign body or diphtheritic paralysis. *Young females* – Hysterical spasm. 30–40 – Achalasia. *Menopause* – Sideropaenic dysphagia. *Above 50* – Carcinoma oesophagus particularly in males.

II. Symptoms—Oropharyngeal dysphagia is usually distinguished from oesophageal dysphagia by the patient's awareness of inability to initiate swallowing properly and occurrence of nasopharyngeal regurgitation, there may also be aspiration of swallowed fluid into the airway.

(1) ***Dysphagia***—(a) *Onset* – Acute in foreign body, encephalitis, thrombosis of cerebellar artery or hysterical. Gradual in stricture, malignancy, achalasia, etc. Onset after shock or emotional upset common in achalasia. (b) *Type of distress* – (i) Difficulty in swallowing both liquids and solids particularly if there is nasal reflux suggests a *neurological condition.* (ii) Difficulty in transferring bolus of food from mouth to gullet is usually caused by *local disorders* of throat, pharynx or larynx. (iii) Sensation of food sticking retrosternally is as a rule due to *oesophageal abnormalities.* (c) *Progress* – Long history with intermittent symptoms in achalasia. Dysphagia first with solids and subsequently fluids suggestive of mechanical obstruction. (d) *Position at which food sticks* – may provide a guide to the site of obstruction as the lesion is either at that level or higher up. (e) *Relation of distress to posture* – If distress at night when patient is in reclining position and relieved in upright position, it suggests oesophageal hiatus hernia. (f) *Deglutition with strangulation or cough* –means central lesions of bulbar type, myasthenia gravis or disease irritating 9th or 10th cranial nerves.

(2) ***Pain***—(i) *Burning, substernal contact pain* is felt when hot, acid, spicy or alcoholic material passes through the inflamed oesophagus. This symptom is virtually diagnostic of oesophagitis. (ii) A prolonged history of heartburn preceding the onset of dysphagia is suggestive of peptic stricture and, less commonly, esophageal adenocarcinoma.

(iii) *Impact pain*—Severe pain substernally when a bolus 'impacts' above a narrowed oesophagus. This type of pain together with sudden dysphagia is characteristic first symptom of encircling carcinoma, occurring less commonly with benign stricture.

(iv) *Spasm pain*—This is severe type of oesophageal pain usually related to muscular spasm (oesophageal colic). Causes are diffuse oesophageal spasm, achalasia, reflux oesophagitis, 'nutcracker oesophagus'.

Table 4: Causes of dysphagia

Acute
• Inflammatory conditions – Pharyngitis, tonsillitis, aphthous ulceration
• Foreign body – Meat bolus, bone or other objects
• Ingestion of caustic substance
Chronic
1. Oropharyngeal
Neurological
• Cerebrovascular accident
• Motor neuron disease
• Parkinsonism
• Myasthenia gravis
• Multiple sclerosis
• Bulbar palsy
• Polyneuropathy
• Dermatomyositis
Infection
• Candida (Fig. 4)
• Herpes
Mechanical or compressive
• Intervertebral disc degeneration
• Postcricoid carcinoma
• Thyroid enlargement
• Aortic aneurysm
• Mediastinal mass
• Mucosal webs
• Pharyngeal pouch
Psychosomatic
• Globus hystericus
2. Oesophageal
Mechanical block
• Carcinoma oesophagus or cardia (Fig. 5)
• Oesophageal stricture
• Mediastinal neoplasm
• Schatzki ring (Fig. 6)
• Zenker's diverticulum (Fig. 7)
• Aberrant great vessels (dysphagia lusoria)
• Eosinophilic oesophagitis
Muscular incoordination
• Achalasia
• Scleroderma
• Diffuse oesophageal spasm
• Chaga's disease
• Oesophagitis – peptic, monilial

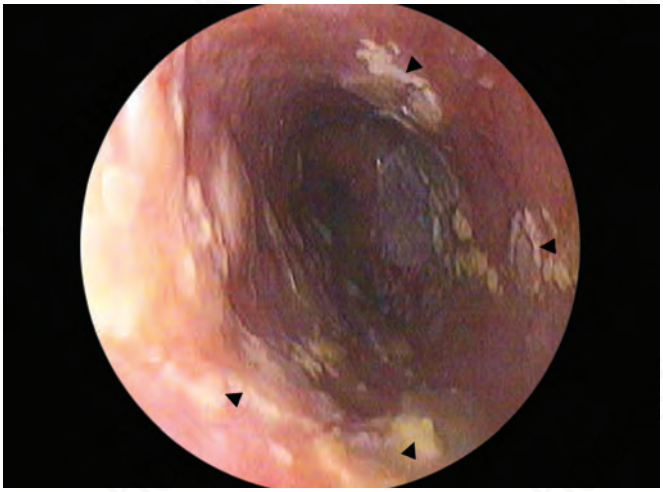


Fig. 4: Oesophageal candidiasis

(3) ***Regurgitation***—Characteristic of long standing achalasia; can occur with stooping or straining in hiatus hernia.

(4) ***Hematemesis***—Oesophagitis, carcinoma.

(5) ***Nasal twang*** and nasal regurgitation of fluids suggests palatal paralysis.

(6) ***Hoarseness of voice***—Carcinoma of larynx. The presence of hoarseness may be another important diagnostic clue. When hoarseness precedes dysphagia, the primary lesion is usually laryngeal; hoarseness that occurs after the development of dysphagia may result from compromise of the recurrent laryngeal nerve by a malignancy.

III. PAST HISTORY – (a) Of swallowing corrosives or of instrumentation suggests benign stricture formation. (b) Of psychoneurotic disorder may suggest globus hystericus. (c) Of cholecystitis or peptic ulcer may point to reflex cardiospasm.

PHYSICAL EXAMINATION

1. *Mouth and throat*—For stomatitis, malignancy tongue and abnormalities of pharynx.
2. *Neck*—Enlarged lymph glands, goitre, malignancy of thyroid.
3. *Chest*—For evidence of aneurysm, mediastinitis or mediastinal tumour, pericarditis, marked cardiac hypertrophy, empyema, and pulmonary abscess.
4. *Nervous system*—For evidence of bulbar paralysis or myasthenia gravis.
5. *Spine*—Cold abscess to exclude chronic retro-pharyngeal abscess.

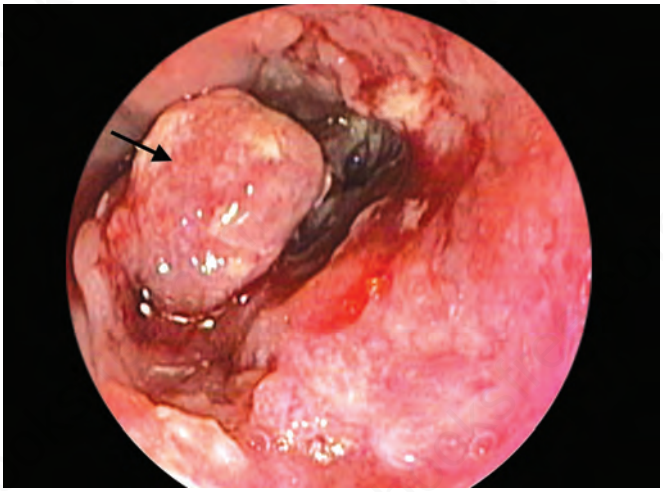


Fig. 5: Carcinoma of oesophagus

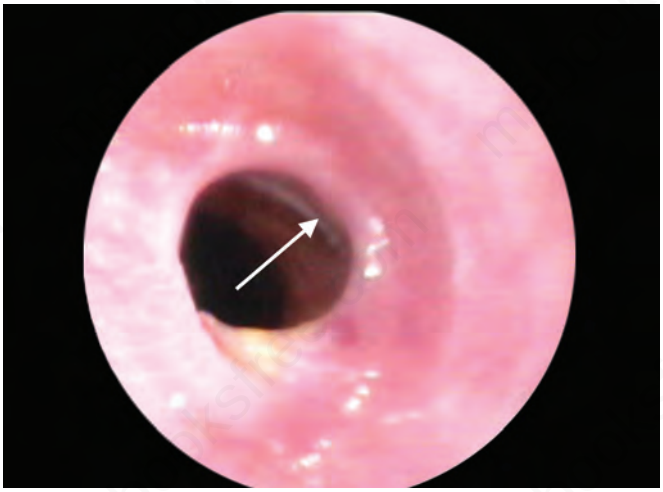


Fig. 6: Schatzki's ring

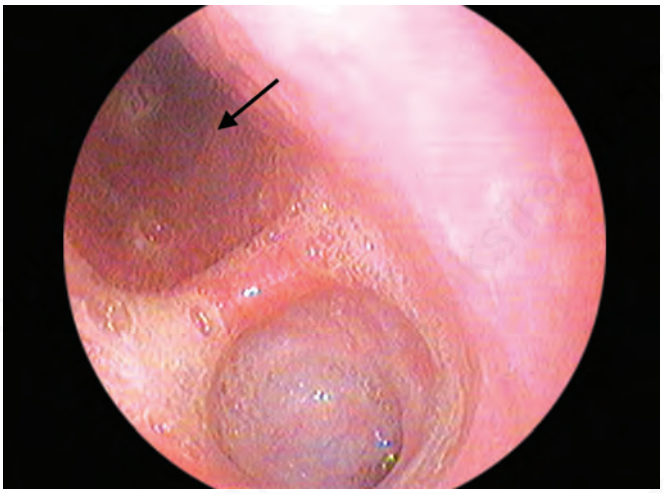


Fig. 7: Zenker's diverticulum

6. *Sideropenic dysphagia*—in Plummer-Vinson syndrome. Dysphagia to solids, iron deficiency, koilonychia, glossitis. Dysphagia is due to a thin web in the precricoid area. The web is formed of degenerated epithelial cells.
7. Skin—changes in the skin may suggest a diagnosis of scleroderma or mucocutaneous diseases such as pemphigoid and epidermolysis bullosa, all of which can involve the esophagus.

INVESTIGATIONS

1. *Laryngoscopy*—Ulceration or growth of larynx.
2. *Barium swallow*—Cardiospasm, stricture, growth, congenital shortening of oesophagus, oesophageal diverticulum.

   Cineradiography with liquid barium and bread soaked in barium may give functional as well as anatomical information about the pharynx and cricopharyngeal segment.

   Videofluoroscopy to investigate chronic dysphagia. It is essentially a modified barium swallow. The three phases of swallowing are observed on a screen and videotaped.
3. *Barium meal*—For hiatus hernia or peptic ulceration.
4. *X-ray chest*—Mediastinal tumour, aneurysm, mitral valve disease. Evidence of lung infection from repeated aspiration in achalasia.
5. *Endoscopy* is the best way to determine the cause of dysphagia because of high diagnostic accuracy and opportunity to take biopsies.
6. *Manometry*—Neither radiology nor endoscopy alone can exclude a treatable motility defect which can readily be demonstrated by intraluminal manometry and pH monitoring. These measure the vigour and coordination of oesophageal muscle contraction patterns, amount of gastro-oesophageal reflux, and the relationship of symptoms to oesophageal luminal events.
7. Biopsy—It is recommended that esophageal mucosal biopsies be obtained routinely in the evaluation of unexplained dysphagia even if endoscopically identified oesophageal mucosal lesions are absent.

TREATMENT

1. Treatment of dysphagia depends on both the focus and the specific etio1ogy.

2. Oropharyngeal dysphagia most commonly results from functional deficits caused by neurologic disorders. In such circumstances, the treatment focuses on utilizing postures or maneuvers devised to reduce pharyngeal residue and enhance airway protection learned under the direction of a trained swallow therapist.
3. Dysphagia resulting from a cerebrovascular accident, Parkinson's disease and amyotrophic lateral sclerosis, may manifest with severe oropharyngeal dysphagia, feeding by a nasogastric tube or an endoscopically placed gastrostomy tube may be considered.
4. Surgical intervention with cricopharyngeal myotomy is used in specific disorders such as the idiopathic cricopharyngeal bar, Zenker's diverticulum and oculopharyngeal muscular dystrophy.
5. The majority of causes of esophageal dysphagia are effectively managed by means of esophageal dilatation using bougie or balloon dilators.
6. Cancer and achalasia are often managed surgically although endoscopic techniques are available for both palliation and primary therapy, respectively.
7. Infectious etiologies respond to antimicrobial medications or treatment of the underlying immunosuppressive state.
8. Eosinophilic esophagitis has emerged as an important cause of dysphagia that is amenable to treatment by elimination of dietary allergens or administration of swallowed, topically acting glucocorticoids.

5. GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease (GORD) is caused by recurrent reflux of gastric contents into the distal oesophagus. The pathophysiology is multifactorial, but dysfunction of the lower oesophageal sphincter (LOS) has a primary role. Motility disorders of the distal oesophagus (e.g. reduced peristaltic amplitude, decreased velocity and increased duration of peristaltic contractions) cause prolonged exposure of the oesophagus to refluxed gastric contents.

Factors which facilitate reflux are listed in Table 5.

Table 5: Factors which facilitate reflux

Mechanism	*Causes*
• Relaxed or hypotonic sphincter	Diabetes mellitus, sliding hiatus hernia, fatty meal
• Decreased LOS pressure	Prolonged gastric tube intubation, scleroderma Drugs – Anticholinergics, β-adrenergic agents, calcium channel blockers, nitrates
• Raised intra-abdominal pressure	Ascites, obesity, pregnancy
• Impaired oesophageal mucosal function	Alcohol, smoking
• Delayed gastric emptying	Pyloric obstruction, fatty foods, gastroparesis
• Increased gastric contents	Large meals, Z-E syndrome

SYMPTOMS AND CONDITIONS ASSOCIATED WITH GERD

Typical symptoms: Heartburn, acid regurgitation.

Atypical symptoms: Dysphagia, globus sensation, non-cardiac chest pain, dyspepsia or abdominal pain.

Extraesophageal symptoms: Hoarseness or sore throat, or both, sinusitis, otitis media, chronic cough, laryngitis or polyps on the vocal cords or both, dental erosions, non-atopic asthma, recurrent aspiration or pulmonary fibrosis, or both.

Sleep related GER can present with multiple awakenings. Substernal burning and/or chest discomfort, indigestion or heartburn. Other symptoms include a sour or bitter taste in the mouth, water brash, coughing or choking.

Malignancy: Oesophageal adenocarcinoma, head and neck cancer.

Barrett's oesophagus is found in 10–20% of patients with reflux oesophagitis, the squamous epithelium is injured by chronic gastro-oesophageal reflux and repair is effected by columnar instead of squamous cells Upper GI scopy (Fig. 8) can be diagnostic assisted by biopsy. This columnar epithelium may undergo malignant transformation.

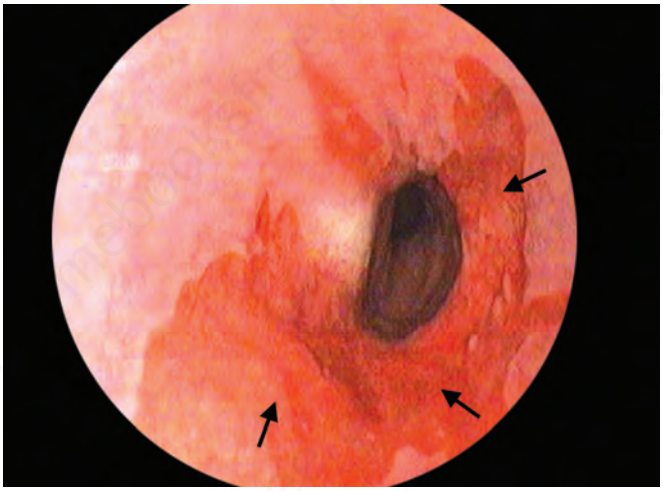


Fig. 8: Barret's oesophagus

INVESTIGATIONS

1. **Radiology**

   Barium swallow with fluoroscopy

   Upper oesophageal sphincter disorders

   Defective opening of pharyngo-oesophageal segment

   Airway aspiration.

   Body motility

   Non-propulsive (tertiary contractions)

   Uncoordinated or weak post-swallow contractions.

   Identification of hiatus hernia, mucosal ulceration, stricture, oesophageal dilatation.

2. **Upper oesophageal endoscopy**

   Indications: GI bleeding, iron deficiency anemia, progressive unintentional weight loss, progressive difficulty swallowing, persistent vomiting, epigastric mass on palpation, suspicious barium meal result or other suspicious imaging result.

3. **Manometry**
   - Upper oesophageal sphincter
   - Tone of upper oesophageal sphincter and relaxation during swallowing.
   - Coordination between relaxation of upper oesophageal sphincter and contraction of the pharynx.
   - Body motility
   - Evaluation of amplitude, duration and velocity of waves.
   - Lower oesophageal sphincter tonic pressure and relaxation.

4. **Oesophageal pH testing**—The ideal standard for oesophageal pH probe replacement is manometric determination EES. Newer technology monitoring of oesophageal pH using a wireless system allowing for data collection for up to 48 hours.
   - Acid reflux time
   - Number and duration of reflux episodes
   - Symptom index. (Percentage of symptom episode associated with reflux episode). Special indications—Atypical symptoms, patient unresponsive to medical therapy, preoperative assessment and follow-up of patient undergoing reflux surgery.

5. **Scintigraphy.** Introduction of technetium^{99} (^{99}Tc) into stomach followed by abdominal compression and radiographic counting over oesophagus. This technique can demonstrate reflux as well as provide quantitative measure of its presence.

MANAGEMENT

1. *Conservative measures*
   - Abstain from eating within 2 hours of bed time
   - Elevate head of bed by 6 inches
   - Sleep in left lateral decubitus position
   - Avoid—Caffeine, nicotine, alcohol, chocolate, mints, carbonated beverages, high-fat foods, tomato or citrus - based products. Avoidance of acidic foods which are inherently irritating.
   - Avoid if possible medications that can worsen GER – Anticholinergic, theophylline, prostaglandin, calcium channel blockers, alendronate.
   - Weight loss if obese (most important of all)
   - Consider nasal CRAP if OSA is present
   - Rabeprazole, esmoprazole provide superior gastric acid suppression.

2. *Acid suppression*—(a) Proton pump inhibitors provide rapid symptomatic relief and healing of oesophagitis in majority of patients. (b) Prokinetic agents such as Tegaserod maleate 6 mg b.d. or Levosulpiride 50 mB.D.d. or Clebopride 0.5 mg b.d. improve motility by increasing LES pressure, accelerating oesophageal acid clearance mechanism and improving gastric emptying.

3. *If no response or relapse*—Test and treat for *H. pylori.* Distal gastritis increases production of gastric acid. In this condition eradication of *H. pylori* reduces risk of acid reflux. Conversely, generalized atrophic gastritis decreases production of gastric acid, as a result *H. pylori* eradication may increase severity.

4. *Surgery*—If persistent non-acid reflux. Antireflux surgery augments the reflux barrier by a full or partial wrap of the gastric fundus (fundoplication) around the lower oesophagus.

6. ACHALASIA OF THE CARDIA

Achalasia (Cardiospasm, Megaesophagus) is a primary motor disorder of the oesophagus. Failure of relaxation of lower oesophageal sphincter on swallowing is a characteristic feature. Degeneration of neuronal cell bodies in the myenteric plexus is thought to be the primary abnormality.

CLINICAL FEATURES

1. ***Dysphagia***—is the dominant symptom. Feeling of obstruction usually of the cardia or sometimes high in the oesophagus. Sensation of food sticking in the oesophagus at first intermittent, later continuous and at every meal, and more with solids.

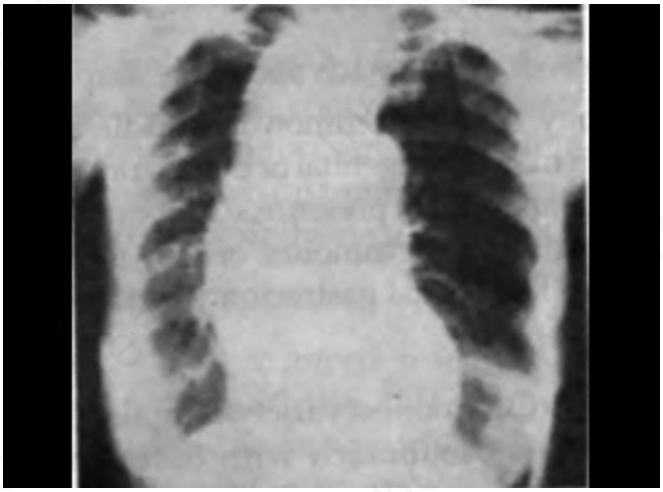


Fig. 9: Chest radiograph showing gross enlargement of the oesophagus due to achalasia

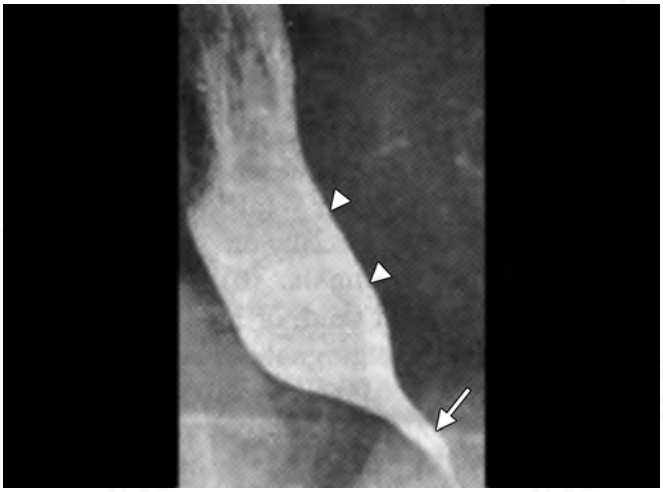


Fig. 10: Barium-filled oesophagus showing distension above (arrow head) the narrow gastro-oesophageal junction
Note: The abrupt narrowing of the lower end of oesophagus (bird beak sign)

2. ***Regurgitation***—In initial stages, food is regurgitated almost immediately following ingestion but as oesophagus becomes dilated, food and secretion may be retained for hours and days followed by delayed regurgitation.
3. ***Chest pain***—Spontaneous retrosternal pain which occurs equally during night and day, is often severe and is relieved by drinking cold water. Patients describe a squeezing, pressure-like retrosternal pain, sometimes radiating to the neck, arms, jaw, and back. Paradoxically, some patients complain of heartburn that may be a chest pain equivalent. Other sensations may be bursting feeling provoked by drinking fast, or sensation of food sticking, and heart burn by lying down or stooping.
4. ***Respiratory symptoms***—(a) Cough and dyspnoea due to pressure on trachea and bronchus by dilated oesophagus. (b) Aspiration may result in aspiration pneumonia, bronchiectasis or lung abscess.
5. ***Asymptomatic***—Occasionally the condition is discovered as a mediastinal swelling on routine chest film.

COMPLICATIONS

1. *Pulmonary*—Fibrosis due to recurrent chest infection.
2. *Carcinoma*—Commonest in mid-oesophagus due to irritation from chronic stasis oesophagitis.
3. *Malnutrition*—Rare.

INVESTIGATIONS

1. *Radiology*—(a) *Plain chest radiograph* will show enlarged mediastinal shadow and oesophageal dilatation with poor emptying and air-fluid level (Fig. 9) (b) *Barium swallow* – Oesophageal dilatation and slow flow into the stomach across a smoothly tapered gastro-oesophageal junction (bird beak sign) (Fig. 10). Absent stomach gas bubble.
2. *Endoscopy*—Usually reveals a chronically inflamed oesophageal mucosa. It has minimal role.
3. *Manometry*—Failure of lower oesophageal sphincter to relax on swallowing. It is the most sensitive diagnostic test.

MANAGEMENT

Pharmacotherapy—Isosorbide dinitrate 5 mg sublingually before meals or nifedipine 10–20 mg have a direct relaxant effect on the muscle of lower oesophageal sphincter. They may be of value while patient is awaiting definitive treatment.

Pneumatic dilatation and extramucosal oesophagomyotomy endoscopy—The aim of both procedures is to effect partial disruption of lower oesophageal sphincter, by stretching it using an inflatable balloon positioned within the oesophageal lumen, or by surgical myotomy at the cardia (Heller's operation). The most significant complication of the operation is gastro-oesophageal reflux.

Endoscopic LES myotomy (*per oral esophageal myotomy*)—This technique involves the creation of a tunnel within the esophageal wall through which the circular muscle of the LES and distal esophagus are transected with electrocautery.

Endoscopic intrasphincteric injection of botulinum toxin—As an alternative to pneumatic dilatation or surgery. It may be of advantage in elderly or frail patients. Multiple treatments are needed over a period of time, but the effect tends to last longer with successive injections.

7. HIATAL HERNIA

Protrusion of the stomach above the diaphragm.

Aetiology—Most common in middle-aged, obese females. It may be congenital or due to conditions which raise intra-abdominal pressure, e.g. obesity, pregnancy, ascites or abdominal tumours, or may follow surgical operations like partial gastrectomy or vagotomy.

TYPES

1. Type I *Sliding*—Commonest variety. Simple upward slide of fundus of stomach with oesophago-gastric junction through the hiatus into the chest.
2. Type II *Rolling* (Paraesophageal)—The oesophagogastric junction is within the abdominal cavity, but part of the gastric fundus protrudes through the hiatus into the thoracic cavity.
3. Type III combined sliding and paraesophageal hernia.
4 Type IV hiatal hernias, viscera other than the stomach herniate into the mediastinum, most commonly the colon.

CLINICAL FEATURES

1. ***Asymptomatic***
2. ***Symptoms due to reflux***—(a) Retrosternal chest pain or discomfort especially on stooping or lying down soon after meals. (b) Heart burn or regurgitation of acid fluid, or food on bending or stooping. Nocturnal regurgitation may cause choking attacks and aspiration pneumonia. (c) Dysphagia due to oesophageal muscle spasm, oesophagitis.
3. ***Symptoms due to pressure***—Either of dilated oesophagus and/or gastric pouch on surrounding structures – (a) From pressure on mediastinum – Dyspnoea, palpitation, cough, anginal pain. (b) From pressure on diaphragm – Hiccup, spasmodic pain.
4. ***Symptoms due to hemorrhage***—Iron deficiency anemia due to massive hematemesis or oozing from oesophageal ulcers.
5. ***Symptoms due to associated diseases***—Peptic ulcer at level of diaphragmatic hiatus, cholecystitis, ischemic heart disease.

In contrast to a sliding hernia, paraesophageal hernia may lead to serious complications, especially strangulation or hemorrhagic anemia.

INVESTIGATIONS

1. *Radiology*—(a) X-ray chest – If a sliding hernia is large, it may be seen as retrocardiac shadow with fluid level. (b) Barium swallow to assess hernia size and development of complications.
2. *Endoscopy and biopsy*—Mainly of value in assessment of oesophagitis and of consequent bleeding, ulceration and stricture formation.
3. *Manometry* is the only sensitive method, as in absence of dilation, barium meal may be reported as normal.

MANAGEMENT

A. Medical

1. *To minimise gastro-oesophageal reflux*—(a) Elevate bed head by 20 cm. (b) Avoid posture precipitating reflux, e.g. bending or stooping forwards, sitting in a low chair. (c) Avoid large meals. (d) No food or drink for 3–4 hours before bedtime. (e) Reduce weight if obese. Stop non-steroidal anti-inflammatory drugs. (f) Avoid foods which provoke symptoms, e.g. pastries, coffee.
2. *Reduce gastric acidity and pepsin secretion* – with ranitidine or famotidine or antacids.

B. Surgical

Surgical correction in resistant cases.

8. DYSPEPSIA

Dyspepsia refers to upper abdominal symptoms usually following intake of food which appears to arise from upper GI tract.

CLASSIFICATION

1. *Organic dyspepsia*: Erosive oesophagitis, gastric erosions, acute or chronic gastritis, gastric ulcer, duodenal ulcer, duodenitis, malignancy (carcinoma, lymphoma). It is suspected in presence of alarm symptoms (wt. loss, anemia, bleeding or positive occult blood, loss of appetite).
2. *Functional or non-ulcer dyspepsia* (see later).

3. *Drug-related*: Aspirin, NSAIDs, antibiotics, bisphosphonates, oestrogens, steroids, digoxin, chloroquine, iron, potassium supplements.
4. *Extra intestinal systemic disease*: Diabetes mellitus, hypothyroidism, hyperparathyroidism, Addison's disease, uremia.

Symptoms of dyspepsia can be divided into:

1. *Reflux type*: Retrosternal burning, regurgitation.
2. *Ulcer type*: Epigastric pain on empty stomach. Relieved with bland food, antacids or acid suppression.
3. *Dysmotility type*: Postprandial fullness, distension, early satiety, nausea.

ROME III DIAGNOSTIC CRITERIA FOR FUNCTIONAL DYSPEPSIA

At least 3 months, with onset at least 6 months previously, of one or more of the following:

- Bothersome postprandial fullness
- Early satiation
- Epigastric pain
- Epigastric burning
- No evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms.

CRITERIA FOR DIFFERENTIATING POSTPRANDIAL SYNDROME AND EPIGASTRIC PAIN SYNDROME

Postprandial Distress Syndrome

1. Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week AND/OR
2. Early satiation that prevents finishing a regular meal, at least several times per week.

Table 6: Potential causes of non-ulcer dyspepsia

• Duodenogastric reflux
• Duodenitis
• Carbohydrate malabsorption (lactose, fructose, sorbitol)
• Cholelithiasis or choledocholithiasis
• Chronic pancreatitis
• Systemic disorders (diabetes, thyroid, parathyroid, hypoadrenalism, connective tissue disease)
• Intestinal parasites
• Psychiatric disorders
• Visceral hypersensitivity
• Gastric/small intestinal dysmotility
• Gallbladder/biliary dysmotility

Supportive Criteria

1. Upper abdominal bloating, postprandial nausea or excessive belching can be present.
2. Epigastric Pain Syndrome may coexist.

EPIGASTRIC PAIN SYNDROME

1. Pain or burning localized to the epigastrium of at least moderate severity at least once per week AND
2. The pain is intermittent AND
3. Not generalized or localized to other abdominal or chest regions AND
4. Not relieved by defecation or passage of flatus AND
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders.

Supportive criteria

1. The pain may be of burning quality but without a retrosternal component.
2. The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting.
3. Postprandial distress syndrome may coexist.

Potential causes of non-ulcer dyspepsia are listed in Table 6.

Differential diagnosis of dyspepsia s given in Table 7.

9. *H. PYLORI* INFECTIONS

H. pylori is a small curved (comma shaped), highly motile Gram-negative organism that colonises only the mucus layer of the human stomach. Multiple strains of the

Table 7: Differential diagnosis of dyspepsia

• Non-ulcer dyspepsia
• Gastro-oesophageal reflux disease
• Peptic ulcer disease
• Medication related: non-steroidal anti-inflammatory drugs, antibiotics, iron, potassium supplements, digoxin
• Carbohydrate malabsorption (lactose, fructose, sorbitol)
• Cholelithiasis or choledocholithiasis
• Chronic pancreatitis
• Systemic disorders (diabetes, thyroid, parathyroid, hypoadrenalism, connective tissue disease)
• Intestinal parasites
• Abdominal malignancy (especially pancreatic and gastric cancer)
• Chronic mesenteric ischaemia

organism exist. It also has considerable genetic heterogeneity, no strains being identical.

Transmission appears to be predominantly via oral faecal route, including contaminated water supplies. Transmission by endoscopy is possible. *H. pylori* infection can be picked up from siblings, older children, or parents predominantly via gastro-oral route.

CLINICAL FEATURES

1. **Gastritis—**Gastric infection with *H. pylori* is the main cause of gastritis. Infection in infancy is thought to lead to pangastritis, whereas in later childhood to predominantly central gastritis.
2. **Peptic ulcer** associated with *H. pylori.* Only a minority of individuals infected with *H. pylori* develop ulcers. Risk of ulceration is increased by cigarette smoking, and by the presence of more aggressive strains of the bacterium that carry the CAGA gene and the S_1 variant of the gene encoding a vacuolating toxin.

PATHOGENESIS

Possible mechanisms for ulcer development:

1. Bacillus secretes urease which converts into ammonia, thus alkalising the surrounding acid medium for its survival but simultaneously producing ammonia-induced mucosal damage. Production of ammonia by bacteria prevents D cells in antral glands from sensing the level of acidity, leading to inappropriate release of somatostatin and an increase in gastrin and thus excess of acid secretion. 2. Neural pathways are affected by *H. pylori* which results in downregulation of acid production. 3. *H. pylori* produces inflammatory response in gastric mucosa with induction of epithelial derived cytokines. Influx of neutrophils and macrophages into gastric mucosa with release of lysosomal enzymes and leukotrienes impairs mucosal defence. 4. *H. pylori* expresses adhesins (OMPs like BabA), which facilitate attachment of the bacteria to gastric epithelial cells.

Role in development of MALT (mucosal associated lymphoid tissue), lymphoma, gastric adenocarcinoma, GERD and dyspepsia.

Mechanisms of gastric ulcer are less well defined, but probably include—1. Local *H. pylori* related inflammation leading to epithelial damage. 2. Inhibition of synthesis of protective prostaglandins by inhibition of cycloxygenase-1 by NSAIDs. 3. Bile reflux, which is increased in these patients.

INVESTIGATIONS

Non-invasive Tests

Serology. The main use of serology is for testing dyspeptic patients in primary care and patients with known ulceration but unknown *H. pylori* status in secondary care. Serology may remain positive for many years after successful eradication of *H. pylori* and is therefore not used for checking the success of treatment.

Urea breath test is a simple, non-invasive test based on the fact that *H. pylori* possesses a powerful urease. It is particularly useful for checking the success of treatment. It must be performed at least 4 weeks after any proton pump inhibitors, bismuth compounds or antibiotics, if not, false-negative results may be obtained.

Biochemical basis of the urea breath test is described in Figure 11.

Stool antigen test is used as ELISA to detect presence of *H. pylori* antigens shed in the faeces. The main advantage of the test is in large scale epidemiological studies of acquisition of *H. pylori* infection in children.

Invasive Tests

Antrum Biopsy

(a) ***Biopsy urease test*** is based on liberation of ammonia by action of *H. pylori* urease. One or two biopsies are placed on a gel or into a solution containing urea with a pH indicator. A colour change is produced if the pH

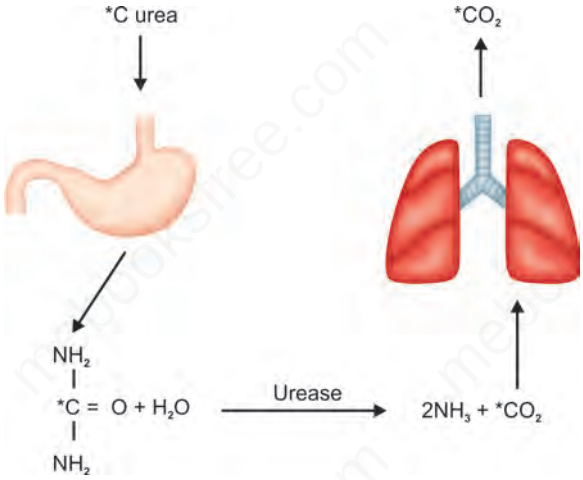


Fig. 11: Urea labelled with the non-radioactive isotope ^{13}C, or very small dose of radioactive ^{14}C, is drunk by the patient If Helicobacter pylori is present in the stomach, its powerful urease catalyses hydrolysis of urea, and labelled carbon dioxide can be detected in breath samples

Table 8: Eradication of H. pylori infection

First-line treatments	
Triple therapy	
1. Bismuth subsalicylate 2 tab qid plus	X 14 days
Metronidazole 250 mg qid plus	
Tetracycline 500 mg qid	
2. Omeprazole 20 mg b.d. plus	
Clarithromycin 250 or 500 mg bid plus	
Amoxicillin 1g b.d. or	
Metronidazole 500 mg b.d.	
3. Ranitidine bismuth citrate 400 mg bid plus	
Tetracycline 500 bid plus	
Clarithromycin or Metronidazole 500 mg bid	
Quadruple therapy	
Omeprazole 20 mg b.d.	
Bismuth subsalicylate 2 tab qid	
Metronidazole 250 mg qid	
Tetracycline 500 mg qid	

Note: An alternative to 'blind' second-line therapy is to culture *H. pylori* and be guided by antibiotic sensitivities.

Table 9: Classification of gastritis

Type of gastritis	*Aetiology*
Non-atrophic	H. pylori
Atrophic	
Autoimmune	Autoimmunity
Multifocal atrophic	H. pylori, ± environmental insults
Special forms	
Chemical	NSAIDs, bile, alcohol
Radiation	Radiation injury
Lymphocytic	Idiopathic, gluten, drugs
Non-infectious granulomatous	Crohn's disease, sarcoidosis, Granulomatous polyangiitis and other vasculitides
Eosinophilic	Food sensitivity
Other infections	Bacteria other than H. pylori (particularly other gastric helicobacter, mycobacteria and syphilis), viruses (cytomegalovirus), fungi (Candida spp., Histoplasma) Capsulatum and Mucoraceae

increases. When *H. pylori* is present, the urea is hydrolysed by its urease, resulting in a colour change. Most tests are read at 24 hours.

(b) ***Histology—H. pylori*** infection can be diagnosed with special stains. Multiple biopsies should be taken from the antrum and corpus.

(c) ***Culture***—Endoscopic mucosal biopsy specimens can be cultured for *H. pylori.* This is not useful as a single diagnostic test, but it enables antibiotic sensitivity testing.

TREATMENT

Eradication of *H. pylori* infection is achieved by regimens given in Table 8.

10. GASTRITIS

Gastritis is inflammation of the gastric mucosa. It can be active or chronic. Gastritis is seldom symptomatic, but can have important clinical sequelae, principally duodenal and gastric ulceration, gastric adenocarcinoma and primary gastric lymphoma. The three important causes of gastritis are *H. pylori* infection, NSAIDs and autoimmunity. Classification of gastritis is given in Table 9.

Chronic gastritis is of two types—Type A and Type B

Type A—Autoimmune gastritis is virtually confined to the corpus and is associated with antiparietal cell and other intrinsic factor antibodies. It may result in vitamin B_{12} deficiency and pernicious anemia and is a risk factor for gastric adenocarcinoma.

Type B—H. pylori can cause antral predominant gastritis, which predisposes to gastric ulceration and distal gastric adenocarcinoma.

NSAIDs/Aspirin cause gastritis characterized by mucosal hyperplasia and oedema but little inflammatory cell infiltration. It may be associated with gastric or duodenal ulceration.

Chemical gastritis due to chemical irritation e.g. reflux of bile or duodenal contents (reflux gastritis).

Treatment—Eradication of *H. pylori*. Patients with pernicious anemia will require parenteral vitamin B_{12} supplementation on a long-term basis.

11. PEPTIC ULCER

The term peptic ulcer applies to mucosal ulceration near the acid bearing regions of the gastrointestinal tract. Most ulcers occur in the stomach or proximal duodenum but they may also occur in the oesophagus (due to acid reflux), in jejunum (at site of gastrointestinal anastomosis), and rarely in relation to ectopic gastric mucosa (near a Meckel's diverticulum).

Table 10: Causes of gastric ulcer
Causes of gastric ulcer
• H. Pylori infection
• NSAIDs
• Neoplasm (carcinoma, lymphoma, lymphosarcoma)
• Stress
• Crohn's disease
• Infections (herpes simplex, cytomegalovirus)
Causes of duodenal ulcer
Common causes
• H. pylori infection
• NSAIDs
Uncommon causes
• Zollinger-Ellison syndrome (Gastrinoma)
• Hypercalcemia
• Granulomatous diseases (Crohn's disease, sarcoidosis)
• Neoplasia (carcinoma, lymphoma, leiomyoma)
• Infections (tuberculosis, herpes simplex, cytomegalovirus)
• Ectopic pancreatic tissue

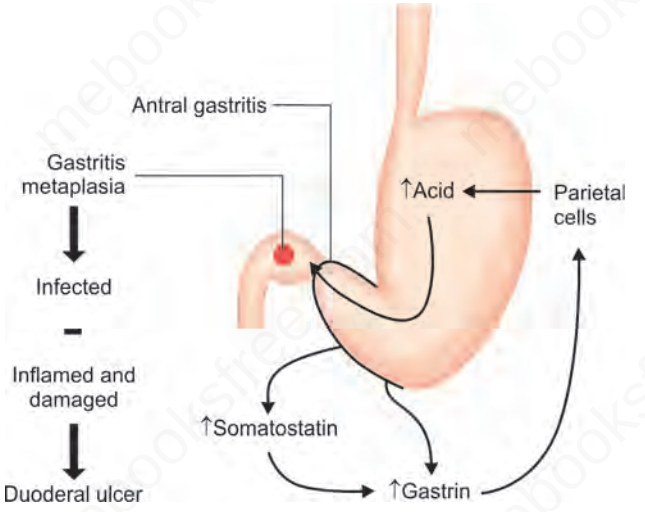


Fig. 12: Antral inflammation leads to reduced somatostatin production and, because somatostatin has a negative feedback effect on gastrin production, this results in hypergastrinemia Gastrin acts on parietal cells, resulting in high stimulated acid production, increased duodenal acid load and the formation of protective gastric metaplasia in the duodenum, *Helicobacter pylori* cannot colonize the normal duodenum, but can colonize gastric metaplasia, causing inflammation and ulceration

AETIOPATHOGENESIS OF PEPTIC ULCER

1. Heredity and strong family history.
2. Peptic ulceration results from digestion of the mucosa with acid and pepsin of gastric juice. Acid secretion is more important in aetiology of duodenal ulcer than gastric ulcer.
3. Mucosal resistance (Gastric mucosal barrier). Mechanism: (a) Secretion of bicarbonate by surface epithelial cells under the influence of mucosal prostaglandins. These cells also secrete mucus that impedes diffusion of ions and molecules such as pepsin. (b) The tight intercellular junctions and surface lipoprotein level provide a mechanical barrier. (c) The submucosal area provides micronutrients and oxygen while removing toxic metabolic products of gastric epithelial cells. (d) Factors reducing mucosal resistance – Drugs like aspirin, NSAIDs, *H. pylori* infection, reflux of bile and intestinal contents into stomach due to poorly functioning pyloric sphincter.

Causes of peptic ulcer are enumerated in Table 10.

Pathogenesis of duodenal ulceration is depicted in Figure 12.

SYMPTOMS – PAIN

1. *Character and intensity*—Variable, usually gnawing, moderate, very mild or severe.
2. *Location and radiation*—Characteristically sharply circumscribed to an area about one inch in diameter between xiphoid and umbilicus. Can occur anywhere in the abdomen, retrosternally, or with a posterior ulcer in the back.
3. *Relation to food*—Rhythmic occurrence and disappearance. Pain invariably absent in morning. Pain usually comes 2–3 hours after meals and is eased by food. Characteristic nocturnal distress between 12 and 2 am. Freedom from pain for about two hours after rising. In gastric ulcer pain is precipitated by food.
4. *Aggravation and relief*—Aggravated by coarse foods, alcohol, nervous tension, undue fatigue. Relief by antacids or after vomiting of acid fluid.
5. *Periodicity of pain*—Most characteristic feature. Even when pain is absent, recurrent bouts of heartburn, anorexia, nausea and vomiting suggest possibility of ulcer.

   Nausea and weight loss occur more commonly in gastric ulcer patients.

Variations in Clinical Picture

1. *From high pain threshold*—Little or no pain, only sensation of fullness or bloating.
2. *Increased reflex activity in gastrointestinal tract*—(a) Oesophageal spasm – Excessive salivation and acid regurgitation (water brash). (b) Pylorospasm – Heartburn.

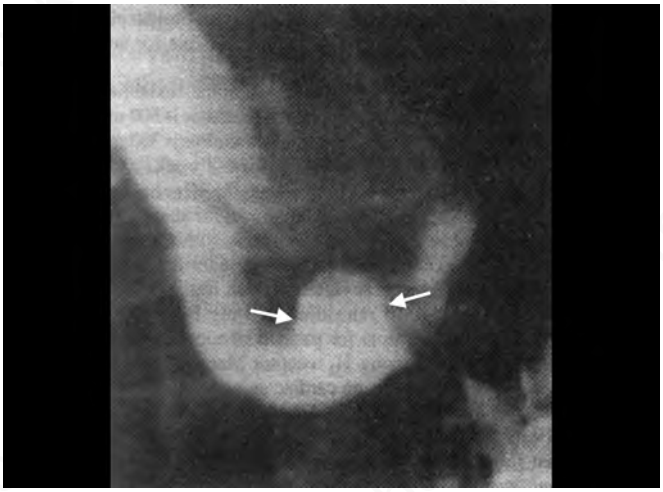


Fig. 13: Barium study demonstrating duodenal ulcer

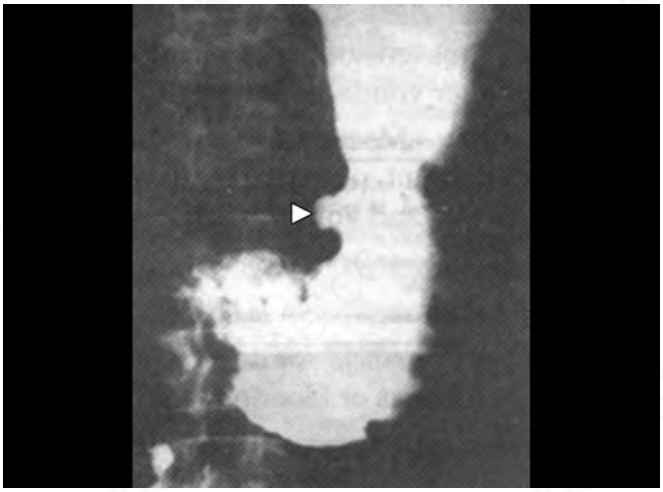


Fig. 14: Barium study of gastric ulcer

(c) Colonic spasm – Features of irritable colon syndrome – Constipation, abdominal pain not related to food and most marked on left side of abdomen.

3. *From complications*—(a) Penetrating ulcer – may cause continuous pain, pain in unusual sites such as back or shoulder and refractoriness to agents formerly yielding prompt relief. (b) Bleeding – acute hematemesis or anemia due to insidious bleeding. (c) Pyloric obstruction – Nausea, anorexia, loss of weight and vomiting. (d) Perforation of ulcer – into lesser sac may cause back pain, malaise and fever.
4. *Postbulbar ulcer*—Mostly back pain, or insidious bleeding.
5. *From associated disease*—Such as gallstones or hiatus hernia.
6. *From neurosis*—Multiple gastrointestinal symptoms due to anxiety.
7. *Acute and stress ulcers*—Aspirin, head injury (causing ulcer by acid hypersecretion, burns and shock), reflux of duodenal contents and mucosal ischemia, severe sepsis, surgery, trauma.

SIGNS

"The history is everything, the physical examination nothing".

1. *Tenderness*—Deep tenderness to the right of the middle in epigastrium. Localised over the site of lesion on deep palpation. Superficial tenderness may be present.
2. *Muscle guarding or rigidity*—may be present with active ulcer or deeply penetrating ulcer.
3. *Peristaltic waves* may be observed in presence of obstruction. Gastric splash may suggest gastric retention due to duodenal ulcer near pylorus.
4. *Occult blood* in stools.

INVESTIGATIONS

1. ***Endoscopy*** is the ideal method of diagnosing duodenal ulcer. The ulcer often appears like a severe aphthous ulcer with a creamy base.
2. ***Barium meal***

Acute stage

- Ulcer crater. Persistent pool of barium.
- Ulcer niche. Crater jutting beyond margins, shown to be on anterior or posterior wall on rolling the patient.
- Irritable duodenal cap seen as spasticity of the cap or a hurry of the barium as it passes through the cap (Fig. 13).

Healing stage

- Radiating folds. Mucosal folds radiating away from the ulcer.
- Scarred and deformed duodenal cap (trifoliate deformity) with multiple ulcers and healing.

Radiographic criteria for benign gastric ulcer (Fig. 14).

- Ulcer crater extending beyond gastric wall
- Gastric folds radiating into base of ulcer
- Thick radiolucent collar of oedema (Hampton's line) surrounding ulcer base.
- Smooth, regular, round or oval ulcer crater
- Pliable and normally distensible gastric wall in the area of the ulcer.

(Up to 8% of GUs that appear to be benign by radiographic appearance are malignant by endoscopy or surgery)

3. ***Gastroscopy.*** In addition to allowing direct visualization of the mucosa, photographic documentation of a mucosal defect and tissue biopsy to rule out malignancy.
4. ***Tests for H. pylori.*** (Refer)
5. ***Gastric studies*** include measurement of basal secretion, or response to injection of histamine, pentagastrin or insulin. Not necessary for assessment of uncomplicated DU, but required only for hypersecretion when patient has continuing DU after gastric surgery.
6. ***Fasting plasma gastrin concentration***—Elevated in Z-E syndrome. Fasting gastrin levels are usually <150 pg/mL. Virtually all gastrinoma patients will have a gastrin level >150–200 pg/mL. Inj. of Secretin in normal individuals causes fall in plasma gastrin, in Z-E syndrome there is immediate rise.
7. ***Hb and MCV***—To exclude anemia of iron deficiency.

COMPLICATIONS

1. Bleeding—Most common
2. Perforation—Acute or chronic perforation into surrounding organs – pancreas, liver, bile duct, colon.
3. Pyloric stenosis.
4. Malignancy at site of ulcer.
5. Pancreatitis due to posterior penetration of ulcer.

DIFFERENTIAL DIAGNOSIS OF DUODENAL ULCER (EPIGASTRIC PAIN)

I. **Gastric lesions**

1. *Gastric ulcer*: See Table 11 for differences between gastric and duodenal ulcer.
2. *Gastric carcinoma* : Clinical features—(a) Dyspeptic symptoms in patient over 45 years. (b) Daily discomfort or pain. (c) Anorexia or undue fullness after meals. (d) Vomiting of small quantities of fresh or altered blood. (e) Weight loss. (f) Unexplained anemia. (g) Previous history of chronic gastritis. (h) Family history of gastric cancer. (i) Known pernicious anaemia. (j) Presence of physical signs such as epigastric mass or jaundice suggest advanced disease. Barium meal examination is useful only for detection of mucosal abnormalities. Neoplastic infiltration causes blunting, fusion, clubbing or tapering of mucosal folds. *Endoscopy and biopsy* with brushing for further confirmation.
3. *Chronic gastritis:* Table 12 gives differentiation between chronic gastritis and peptic ulcer.

II. **Duodenal lesions**

1. *Pseudoulcer syndrome* (Pyloroduodenal irritability) —Discomfort later after meals, relieved temporarily by food or antacids, and in many cases typical periodicity of remissions and relapses. Often hyperchlorhydria. X-ray studies show pylorospasm and extreme irritability of duodenal cap. No evidence of ulcer.
2. *Duodenitis*—Often no pain but nausea and sensation of fullness in upper right part of abdomen. Maximum intensity several hours after ingestion of food. Symptoms are usually not intermittent but continuous. Endoscopy shows inflamed, hemorrhagic or friable duodenal mucosa.
3. *Duodenal diverticula*—Pain in epigastrium, may arise ½ to 2½ hours after meals. Not relieved by diet or antacid. Diverticula seen on barium meal X-ray.

Table 11: Differences between gastric and duodenal ulcer

	Gastric ulcer	*Duodenal ulcer*
Course of illness	Less remittent	More remittent
Pain	Longer duration	Shorter duration
Food	Provokes the pain	Relieves the pain
Heart burn	Less common	More common
Antacids	Relief of pain not instant	Prompt relief of pain
Anorexia, nausea	More common	Less common
Spontaneous perforation	Less common	More common

Table 12: Differentiation between chronic gastritis and peptic ulcer

Chronic gastritis	*Peptic ulcer*
History of repeated attacks of acute gastritis	History of ingestion of NSAIDs
Pain slight, more soreness	Pain usually severe
Pain intensified by food, no pain if meal is delayed	Food may relieve pain
Pain relatively constant	Intermissions
Symptoms of indigestion	Few symptoms of indigestion marked
Slight or no hemorrhage	Profuse hematemesis
Endoscopy – Patchy	Endoscopy – Ulcer with
mucosal irregularity	creamy base

4. *Carcinoma of duodenum*—Very rare. Older patient. Symptoms of short duration and severe. No intermittency of symptoms; no relief by medical treatment. Later signs of obstruction, hemorrhage or jaundice. Mass may be felt.

III. **Gallbladder disease**

Chronic cholecystitis—Vague upper abdominal distress and fullness after meals. Belching and eructations. Intolerance of fat. Attacks of epigastric pain with tenderness over gallbladder. No occult blood in stools. Biliary colic and jaundice due to complicating gall-stones. Symptoms tend to be more irregular and less periodic. Ultrasound confirms diagnosis.

IV. **Pancreatic disease**

1. *Chronic calcifying pancreatitis*—Upper abdominal pain continuous or intermittent, weight loss, steatorrhoea, diabetes. Jaundice due to involvement of common bile duct late manifestation. Plain radiograph of abdomen may show pancreatic calculi.
2. *Carcinoma of pancreas*—Mid-epigastric pain steady and dull, or paroxysmal colicky pain. Relief from pain may be obtained by stooping or bending or lying in bed with knees tightly drawn up into the abdomen (jack-knife position). Jaundice may be present. Peripheral oedema and thrombophlebitis are recognised presentations. Weight loss and anorexia. Rapidly progressive. Evidence of metastasis in liver or elsewhere.

V. **Diseases of colon**

1. *Carcinoma*—Pain on right side below level of umbilicus. Lump may be palpable. No response to medical regime. Filling defect on radiography.
2. *Chronic appendicitis*—Dyspepsia more or less continuous. Irregular short attacks of sharper pain. Nausea common. Vomiting. Pain worse on exertion, unrelated to ingestion of food. Pain mid-epigastric but often radiates to right iliac fossa.
3. *Ileocaecal tuberculosis*—May produce reflex dyspeptic symptoms. Constipation alternating with diarrhoea. Thickening or lump in right iliac fossa.
4. *Irritable bowel syndrome*—Postprandial type of pain related to meals may occur. Pain often relieved by defecation. May be accompanied by abdominal fullness, bloating or flatulence. Alternating constipation and diarrhoea in majority. Faeces characteristically ribbon-like with often excessive mucus.

VI. **Superficial or radicular pain**—Pain usually constant. Hyperaesthesia of abdominal skin. Flexion of abdominal wall reveals situation of pain.

VII. **Functional dyspepsia**—Postprandial fullness, early satiation, epigastric pain or burning in absence of causative disease to explain the symptoms.

VIII. **Miscellaneous**

1. *Hiatus hernia*—Chronic heart burn, intermittent regurgitation, dysphagia and substernal or epigastric pain aggravated by stooping or lying flat. Duodenal ulcer is often found with hiatus hernia which is also more common in women. Barium examination will show intrathoracic herniation of stomach.
2. *Ankylostomiasis*—Mild but continuous epigastric pain or discomfort. Anemia. Hookworm ova in stool.
3. *Epigastric hernia*—Eructations, nausea and vague abdominal discomfort. Epigastric pain may be aggravated or relieved by change of posture. Hernia in the linea alba above the umbilicus.
4. *Visceroptosis*—Symptoms variable and many. Pain worse after food. Pain arises during meals and increases as more food is taken. Accompanying sensation of fullness, distension, feeling of weight or dragging in epigastrium. Discomfort persists for hours often with belching and regurgitation. Antacids without effect. Weak abdominal wall. Glenard's test – On standing behind the patient, raising lower abdomen with both hands and holding it up in that position, there may be some relief.
5. *Abdominal angina*—Due to chronic intestinal ischemia. As in effort angina, the pain of intestinal ischemia develops with maximal work load following meals: (i) Occurs usually in patients over 40 years of age. (ii) Post-prandial abdominal pain, usually cramping and referred to the back, develops 20 to 30 minutes after meals and lasts 1 to 2 hours. (iii) Progressive weight loss due to anorexia and malabsorption. (iv) Constipation common, may be interrupted occasionally by steatorrhoea. (v) Central abdominal bruit with at times absent peripheral pulses. (vi) X-ray studies with barium may show puddling of barium in small bowel as a result of impaired motility. (vii) Stool – Excessive fat and often occult blood. (viii) Aortography with exposure of the film in the lateral projection will demonstrate the occlusive process in the coeliac and superior mesenteric arteries.
6. *Gastrinoma*—Triad of abdominal pain, weight loss and diarrhoea.

Medical management of peptic ulcer

INDICATIONS

1. Short history (less than 5 years) and few relapses.
2. Mild symptoms.
3. Good social and economic position.
4. No radiological evidence of penetrating ulcer, pyloric stenosis or marked duodenal deformity.
5. General condition unsuitable for surgery.
6. Few chances of recovery after removal of organic lesion due to marked neurosis.

1. **Rest:** Physical and mental. Rest in bed during acute phase and for one week after subsidence of pain.

   Indications for hospitalization—(i) Tarry stools or strongly positive occult blood reaction. (ii) Constant pain replacing previous ulcer rhythm. (iii) Gastric retention. (iv) Uncontrollable night pain or vomiting. (v) Suspicion of impending perforation.
2. **Diet:** Bland diet. Duration of particular phase of diet will depend on severity of symptoms, constitution, response to treatment and co-operation of patient. 3-hourly feeds throughout the day – small, digestible, but of adequate caloric value form the basis of treatment.
3. **Pharmacotherapy**
   See Table 13 for drug treatment of peptic ulcers.
4. **Relief from anxiety and mental stress:** Ulcer symptoms get aggravated during periods of mental stress. Psychotherapy and antidepressant like Doxepin 7.5 mg/day.
5. **Avoidance of gastric irritants and stimulants—** Tobacco, alcohol, coffee, tea, sour fruits, meat extracts, ulcerogenic drugs.

Table 13: Treatment of peptic ulcers

Drugs used for peptic ulcer		
Drug	*Dosage*	*Side effects*
H_2-receptor antagonists		
Ranitidine	150 b.d. or 300 mg nocte	Headache, confusion (reversible)
Famotidine	40 mg b.d. or 80 mg nocte	Headache, dizziness
Antacids		
Aluminium hydroxide	300 mg 2–3 hours after	Constipation. Long-term use
Magnesium hydroxide	40 mg a meal	depletes body of phosphates
Alginic acid	500 mg	Laxative effect
Mucoprotective drugs		
Prostaglandin analogues		Contraindicated in women of child bearing age.
Misoprostol	200 mg qds.	Abdominal pain, diarrhoea (more useful for NSAIDs induced gastritis)
Sucralfate	1 g qds. before meals	Constipation
Mosapride	5 mg b.d.	Headache
Colloidal bismuth	240 mg b.d. before meals	Stains tongue and teeth
Proton-pump inhibitors		
Omeprazole	20 mg	
Lansoprazole	20 mg	
Pantoprazole	20 mg on empty	Hypergastrinemia,
Rabeprazole	20 mg stomach o.d.	diarrhoea. Headache
Esmoprazole	40 mg	Skin rash
Eradication of H. pylori	(see H. pylori)	
Anticholinergics		
Probanthine	15 mg t.d.s.	Dryness of mouth.
Pirenzepine	50 mg b.d.	Blurring of vision
		Given as adjuvant to H_2-receptor antagonists as bedtime dose

PREVENTION OF RECURRENCE

1. ***Education of patient***—(a) About recurrent nature of disease. (b) Avoid tobacco, coffee, tea, alcohol, hurried meals, raw vegetables and fruits, fried food, meat extracts, condiments and spices. (c) No emotional stress. (d) Regular hours of rest and sleep. (e) Avoid excessive fatigue. (f) Avoid drugs which might reactivate ulcers, such as aspirin, NSAIDs, steroids.
2. ***Dietary management***—With interval feedings. Snacks between breakfast and lunch and lunch and dinner and a glass of milk before retiring. Snacks may consist of biscuits, toast, or chapattis with or without butter, sandwiches, light cake, curds, butter milk, milk, ice cream, custard or pudding.
3. ***Psychotherapy***—When indicated.
4. ***Preparedness***—Intensified therapeutic regime on exposure to circumstances known to aggravate ulcer – (a) Acute respiratory infection. (b) Excessive work or severe fatigue. (c) Insomnia and nervous irritability due to emotional tension.

Table 14: Indications for surgical treatment of peptic ulcer
• Pyloric stenosis
• Perforation, acute and chronic
• Recurrent bleeding or severe hemorrhage
• Evidence of penetrating or adherent ulcer
• Intractability and relapses
• Severe persistent hour-glass deformity
• Very large ulcers
• Combined gastric and duodenal ulcers
• Suspicion of malignancy
• Economic consideration

Indications for Surgical Treatment

Table 14 lists indications for surgical treatment of peptic ulcer.

ZOLLINGER-ELLISON SYNDROME

Severe peptic ulcer secondary to gastric acid hypersecretion due to unregulated gastrin release from a non β-cell gastrinoma. Gastrinomas are classified into sporadic tumors (more common) and those associated with multiple endocrine neoplasia (MEN) type 1. Gastrin stimulates acid secretion through gastrin receptors on parietal cells by inducing release of histamine from ECL cells. Hypergastrinemia is responsible for the clinical manifestations of ZES.

Clinical Features

(a) *Peptic ulcers* with atypical locations (second part of duodenum and post bulbar (jejunum). Ulcers resistant to medical therapy, recurrence after acid-reducing surgery. Ulcers presenting with complications (bleeding, perforation or obstruction). (b) *Oesophagus* – Mild oesophagitis to frank ulceration and Barrett's mucosa. (c) *Diarrhoea* results from volume overload on small intestine, inactivation of pancreatic enzymes by acid which also damages intestinal epithelial surface. (d) *Signs of hyperparathyroidism* or hypophyseal or pancreatic tumour (MEN 1 syndrome).

Diagnosis: Biochemical Tests

Fasting gastrin level >150–200 pg/mL (Normal <150 pg/mL). If normal or elevated requires additional tests. (b) 1. Gastrin provocative tests—An increase of 120 pg within 15 min of secretin injection has very high sensitivity. 2. Barium meal shows coarse mucosal folds and ulcers.

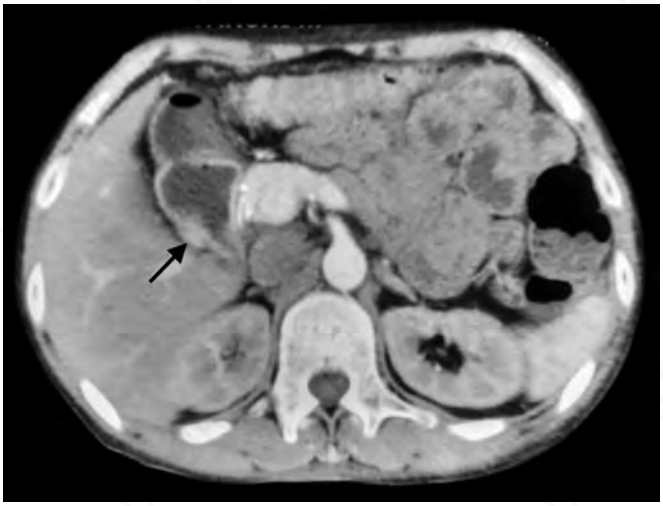


Fig. 15: Gastrinoma in D2 wall

3. Tumour localization—EUS and imaging of pancreas with endoscopic exploration of duodenum for primary tumours. Localization of gastrinomas by measuring the uptake of the stable somatostatin analogue 111In-pentreotide (OctreoScan) is possible. CT scan (Fig. 15), MRI to exclude metastatic disease.

Management

(a) Omeprazole 60 mg/day in divided doses over 24 hours. (b) Octreotide as adjuvant therapy if peptic symptoms difficult to control with PPI. (c) Surgical resection of tumour. (d) Chemotherapy for metastasis.

Table 15 lists hormones secreted by alimentary system.

Table 16 lists causes of intestinal ulcers.

12. GASTRIC CANCER

The most common malignancy of the stomach is gastric adenocarcinoma. Factors associated with gastric cancer are listed in Table 17.

CLINICAL FEATURES

Patient may present with:

- Indigestion (most common presentation)
- Weight loss
- Nausea
- Vomiting
- Hematemesis
- Melena

Table 15: Alimentary hormones

Hormone	*Physiological role*
Gastrin	Stimulates acid, maintains mucosal growth, causes gastric motor activity
Secretin	Stimulates pancreatic bicarbonate
Cholecystokinin	Stimulates GB contraction and pancreatic enzyme secretion
Motilin	Causes upper alimentary motor activity
Glucose-dependent insulin releasing hormone	Stimulates insulin release
Neurotensin	Unknown
Enteroglucagon	Maintains mucosal growth. Slows intestinal transit
Pancreatic polypeptide	Inhibits GB contraction and pancreatic enzyme release

Table 17: Factors associated with gastric cancer

Genetic factors
• Family history (10% of patients)
• Blood group A
Environmental and dietary
• Salted pickles and smoked meat and fish.
• Environmental nitrates/nitrites[#]
• High concentration of lead and zinc in drinking water
• Cigarette smoking
• Consumption of neat spirits
• Poor-quality diets low in vitamin C and high in starch
• Workers in metal, clay and paint industries
Infection
• H. pylori[$]
Premalignant conditions
• Chronic atrophic gastritis
• Intestinal metaplasia
• Benign gastric ulcer
• Gastric adenomatous polyps
• Previous gastric surgery
[#] converted to nitrosamines by gastric bacteria.
[$] high gastric pH encourages bacterial overgrowth, converting nitrites to nitrosamines.

- Profound anorexia
- Flatulence
- Metastatic disease—Palpable left supraclavicular node, metastatic nodules to the ovary (Krukenbergs tumour), periumbilical region ("Sister Mary Joseph node") or peritoneal cul-de-sac (Blumer's shelf palpable on rectal or vaginal examination), ascites, jaundice, palpable abdominal mass, enlarged liver.

Table 16: Causes of intestinal ulcers

• Amoebiasis
• Inflammatory bowel disease
• Bacillary dysentery
• Tuberculosis
• Z-E syndrome
• Malignant ulcers
• Mesenteric artery occlusion
• Ischemic colitis

INVESTIGATIONS

1. *Radiology*—Double contrast studies to detect mucosal abnormalities due to neoplastic infiltration.
2. *Endoscopy*—Multiple biopsies from the margins and brush cytology from the base and under the edges (Fig. 16).
3. *Laparoscopy*—For detection of local and peritoneal spread, and endoluminal ultrasonography for assessing local invasion and lymph node metastasis.
4. Abdominal CT—This and delineate and show metastatic spread (Fig. 17).

MANAGEMENT

Surgery—In early cases local gastric resection, in more advanced disease subtotal or total gastrectomy. Chemotherapy in patients with inoperable disease.

13. HEMATEMESIS AND MELAENA

Hematemesis indicates a site of bleeding proximal to duodenal-jejunal junction, because blood entering the gut distal to this point seldom returns to the stomach (Table 18). The colour of the blood depends on whether the blood has been in the stomach, a large volume of bright red blood suggests a rapid and sizable hemorrhage, whereas a small amount of dark blood (coffee grounds) is more suggestive of a smaller bleed that has been altered by contact with gastric acid.

Melena stools have a characteristic black, tarry appearance and foul smell. Melena occurs when more than 60 mL

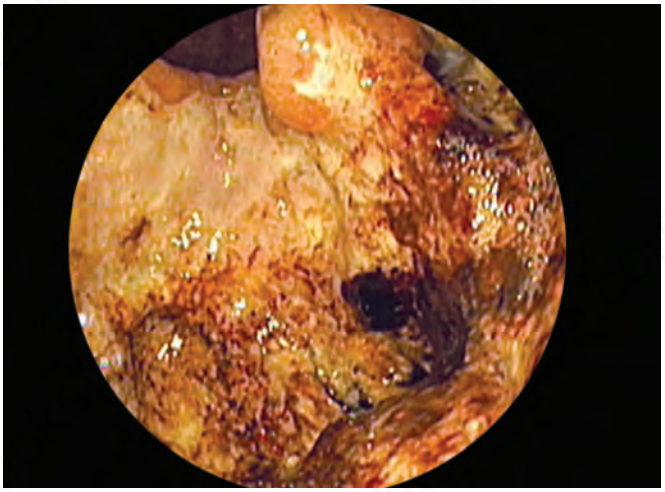


Fig. 16: Carcinoma of stomach

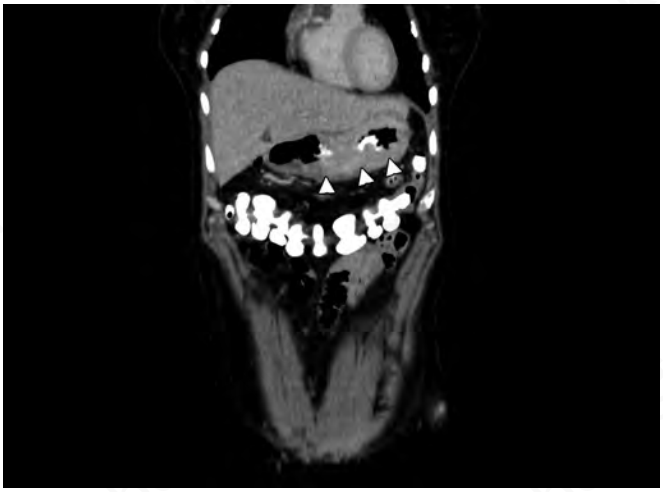


Fig. 17: Linitis plastica: stomach wall thickening

Table 18: Causes of haematemesis and melena
Oesophagus
• Oesophageal varices
• Mallory-Weiss tear
• Oesophageal carcinoma
• Reflux oesophagitis
• Foreign body
Stomach
• Peptic ulcer
• Erosive gastritis
• Portal hypertensive gastropathy
• Gastric carcinoma
• Lymphoma
• Leiomyoma
• Angiodysplasia
• Dieulafoy's erosion (ruptured ectatic submucosal artery)
Duodenum/jejunum
• Peptic ulcer
• Erosions/duodenitis
• Vascular anomalies (AVMs)
• Hemobilia
• Polyps (including Peutz-Jeghers syndrome)
• Aortoduodenal fistula
• Mesenteric arterial occlusion

Table 19: Causes of massive upper GI bleeding
Oesophageal or gastric varices
Gastric ulcer
Duodenal ulcer
Stress ulceration
Dieulafoy's erosion
Aortoenteric fistula

of blood is lost into the upper GI tract. Melena indicates that blood has been present in the GI tract for at least 14 hours (and as long as 3–5 days). Lesions in the oesophagus, stomach and duodenum are responsible for most cases, but occasionally hemorrhage into small intestine, or even the right colon can cause melena if GI transit is slow. Massive upper GI bleeding (Table 19) may result in passage of dark red stools because of rapid transit.

Dieulafoy's disease is a rare cause of massive upper GI hemorrhage in previously asymptomatic individuals. The disease is characterised by a large thickened artery which follows a tortuous course towards the surface mucosa of gastric fundus, duodenum or jejunum. At endoscopy, the appearance of arterial spurting from otherwise normal mucosa is typical.

MANAGEMENT OF BLEEDING

Primary care (before hospital admission)

- IV access with infusion of normal saline
- Oxygen
- Early hospitalization

Hospital management

- *Resuscitation*

  Insertion of large bore cannula into a substantial vein.

If pulse rate > 100/min or systolic BP falls below 100 mm Hg – infusion of crystalloids such as normal saline is started.

If blood transfusion is required, 2–4 units of whole cross-matched blood. Aim is to maintain Hb concentration of 10g/dL.

After resuscitation

- *Endoscopy* must be done within 24 hours and is necessary for—Diagnosis in order to plan treatment.

  Prognosis—Endoscopic stigmata are very useful by defining risk of further bleeding.

Investigation of upper GI bleeding

HISTORY

- *Vomiting or retching*—Before the episode characteristic of Mallory-Weiss syndrome (Fig. 18).
- *Heart burn and regurgitation*—Reflux oesophagitis.
- *Dysphagia and weight loss*—Oesophageal malignancy
- *History of peptic ulcer or abdominal pain*—History of peptic ulcer is useful. However, bleeding can be the first manifestation of an asymptomatic ulcer.
- *Drugs*—Intake of aspirin or NSAIDs.
- *Alcohol intake*—Questioning for alcohol consumption and other risk factors for chronic liver disease.
- *History of easy bleeding or bruising*—Coagulation or platelet disorders.
- *Haematemesis with melena*—Indicates that the source of bleeding must be proximal to the jejunum.

EXAMINATION

Rapid assessment of hemodynamic state

- Does the patient look pale or shocked?
- Pulse rate and BP.
- Postural hypotension.
- Presence of purpura or petechiae—Telangiectasia of Rendu-Osler-Weber syndrome. Palpable purpura characteristic of systemic vacuities, and perioral pigmentation of Peutz-Jeghers syndrome (uncommon causes).
- Splenomegaly, dilated abdominal veins or ascites—Signs of portal hypertension in patients bleeding from gastric or oesophageal varices. A congested gastric mucosa (portal hypertensive gastropathy) can also be a site for GI hemorrhage in patients with liver disease.
- Presence of jaundice—Triad of biliary colic, jaundice and melena suggests hemobilia.

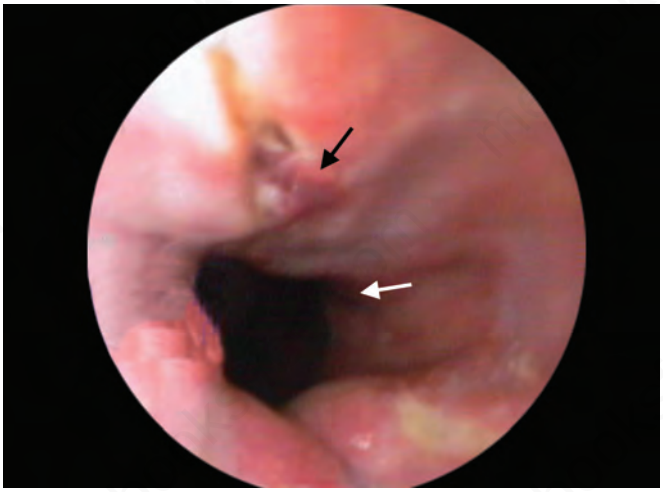


Fig. 18: Mallory-weiss tear

INVESTIGATIONS

Blood tests

- *Hemoglobin concentration*—In first few hours after a bleed is a poor indicator of blood volume loss, because dilution by extracellular fluid recruited into the intravascular space may continue for more than 24 hours Low Hb at presentation usually signifies chronic blood loss.
- *Urea and electrolytes*—Elevated blood urea suggests severe bleeding.
- *Liver function tests*
- *Prothrombin time*

Further investigations—In a few individuals endoscopy does not define the cause of bleeding, because blood in the lumen prevents adequate inspection of the mucosa. If no cause is found – endoscopy can be repeated. If there is still no diagnosis and bleeding continues –

Small bowel imaging. Capsule endoscopy is recommended as a diagnostic test after a normal endoscopic evaluation of upper and lower GI tract after a negative gastroscopy and colonoscopy in patients with obscure GI bleeding.

Labelled RBC scan can detect rates of blood loss as low as 0.1 mL/min.

Angiography/CT angiography does not detect bleeding at rates below 1mL/min, but occasionally reveals underlying vascular abnormalities. Both investigations may fail to localise the site of hemorrhage if it is intermittent.

MANAGEMENT

Procedures to stop bleeding are listed in Table 20.

Table 20: Procedures to stop bleeding

Non-variceal hemorrhage	*Variceal hemorrhage*	
1. **Endoscopic therapy** to seal the arterial defect created by the ulcer. Indications: (a) Bleeding oesophageal varices. (b) Peptic ulcer with major stigmata of recent hemorrhage. (c) Vascular malformations, including actively bleeding AVMs, gastric antral vascular ectasia and Dieulafoy's lesion. (d) Rarely, active bleeding from a Mallory-Weiss tear. *Injection*: (a) Adrenaline 1:10,000 (b) Fibrin glue, a mixture of thrombin and fibrinogen (injected through separate channels) and human thrombin are effective and have a low complication rate. *Heat energy*: Devices are applied directly to the bleeding point to cause coagulation and thrombosis. The heater probe is pushed firmly on to the bleeding lesion to apply tamponade and defined pulses of heat energy are then given to coagulate the vessel. *Mechanical devices*—'Endoclips' can be applied to bleeding vessels and are the best treatment for major bleeding ulcers. *Re-bleeding after endoscopic therapy* requires operative interavention.	*Vasoactive drugs*	
	Vasopressin	20u over 20 min + 0.4u/min. infusion
	Glypressin	2 mg every 6 hrs
	Octreotide	50 mg bolus + 50 mg/h infusion
	Somatostatin	250 mg bolus + 250 mg/h infusion
	Glyceryltrinitrate	40–400 mg/min infusion
	Terlipressin	2 mg bolus every 4-6 hours.
	• ***Modified Sengstaken Blakemore*** (Minessota) **tube insertion** (Both temporary measures)	
	• ***Propranolol*** *up to a dose to reduce pulse rate by 20% to reduce risk of rebleeding*	
2. **Drug therapy**—To reduce risk of further bleeding. *Gastric acid lowering drugs*—Omeprazole 80 mg bolus followed by 8 mg/hr infusion for 72 hours. *Tranexamic acid*—A antifibrinolytic agent can improve stability of the clot and reduce risk of re-bleeding.	• ***Endoscopic treatment*** Injection sclerotherapy – Intravariceal injection of sclerosant (5% ethanolamine, 1% olidocanol). Complications include oesophageal ulceration, fever, pleural effusion, pericarditis. Injection of fibrin glue.	
3. **Emergency surgery if**: (a) Active bleeding cannot be controlled by endoscopic treatment. (b) Re-bleeding follows initially successful endoscopic treatment.	• ***Variceal banding*** **Oesophageal band ligation**. Banding obliterates varices more efficiently and has few complications, but may be more difficult to perform in patients with active bleeding.	
	• ***Shunt surgery***. *Use of small-bore 8 mm interposition H-graft portocaval shunt reduces incidence of encephalopathy.*	
	• ***Devascularization surgery*** *if failure of non-operative treatments and patients who cannot undergo shunt surgery or TIPSS.*	
	• ***TIPS*** *reduces rebleeding rates compared to endoscopic therapy.* Covered stents are used to improve patency.	

14. LOWER GASTROINTESTINAL HAEMORRHAGE

Table 21 lists causes of acute lower GI haemorrhage.

CLINICAL FEATURES AND DIAGNOSIS

Initial assessment: Patients usually present with bright red rectal bleeding (signifying a distal lesion) or dark red rectal bleeding which may be mixed with mucus in case of inflammatory or neoplastic lesion.

Past history of abdominal pain and alteration of bowel habit may suggest a neoplastic lesion, diarrhoea and urgency of defecation inflammatory lesion. Radiotherapy for genitourinary malignancy can cause radiation colitis. Elderly patients with cardiovascular disease may have ischemic colitis.

Table 21: Causes of acute lower GI haemorrhage

Anorectal conditions
• Haemorrhoids
• Anal fissure
• Mucosal prolapse (Solitary rectal ulcer syndrome)
Children
• Meckel's diverticulum
• Juvenile polyps
• Inflammatory bowel disease
Adults
• Inflammatory bowel disease
• Adenomatous polyps (Fig. 19)
• Carcinoma

Contd...

Contd...

- A-V malformation
- Meckel's diverticulum

Elderly

- Diverticular disease
- Angiodysplasia
- Adenomatous polyps
- Carcinoma
- Ischemic colitis
- Inflammatory bowel disease

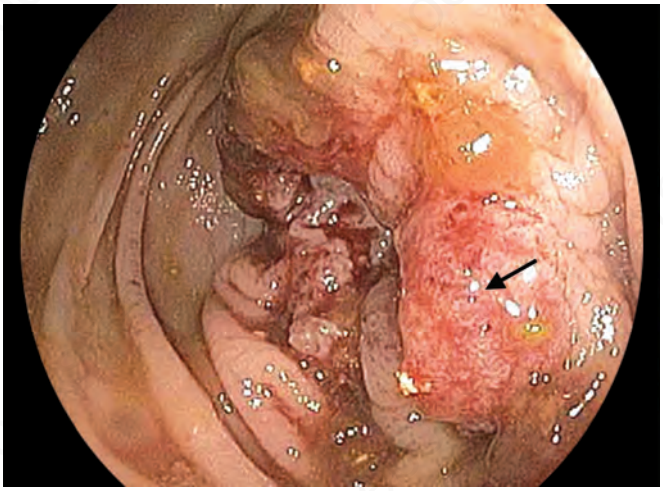


Fig. 20: Rectosigmoid growth

History of dyspepsia, alcoholism, NSAID ingestion or weight loss may give clues to the causative lesion.

MANAGEMENT

Initial Management

1. Hospitalization if suspicion of significant bleed.
2. Correction of hypovolemia with plasma expanders followed by blood transfusion. Central venous pressure or Swann-Ganz monitoring helps prevent over transfusion in the elderly and is a sensitive indicator of continued or recurrent bleeding.
3. Blood for Hb, clotting screen and urea and electrolyte estimation.

Investigations—May be planned after resuscitation. Digital anorectal examination and proctosigmoidoscopy (Fig. 20) to exclude local anorectal conditions and rectal biopsy plus stool microscopy and culture. Upper GI endoscopy if a local cause is not found. Capsule endoscopy is useful in detection of small bowel lesions in Crohn's disease, non-steroidal anti-inflammatory drug enteropathies, small bowel polyposis syndromes and small bowel tumours.

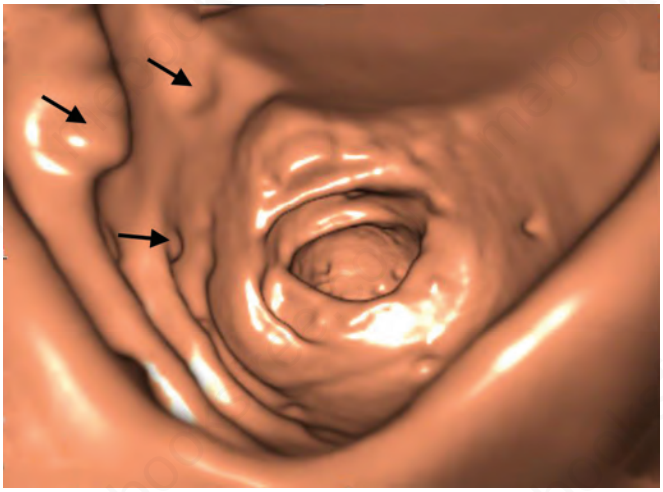


Fig. 19: Virtual colonoscopy showing colonic polyps

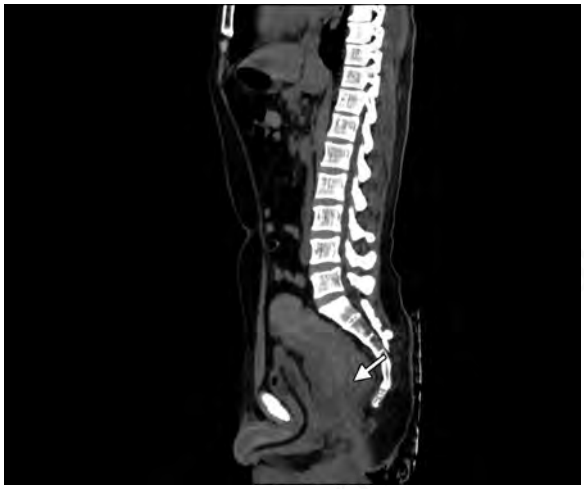


Fig. 21: Lower GI bleed: Non-enhanced CT abdomen showing rectal haematoma

CT angiography may be helpful in locating bleeder (Figs. 21 and 22).

Emergency laparotomy if hemorrhage is massive and patient is deteriorating; this should be combined with on-table colonoscopy.

Occult GI bleeding—Bleeding that is not visible and is manifested by positive faecal occult blood (FOB) testing or iron deficiency anemia.

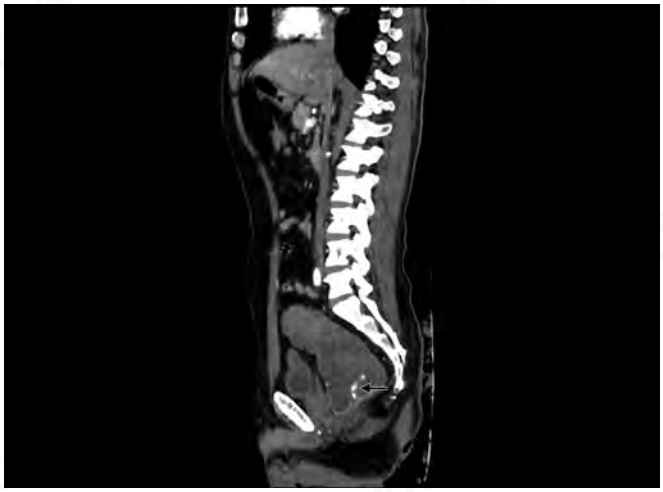


Fig. 22: Lower GI bleed: Contrast CT abdomen showing bleeding spurt in rectum

Physical examination findings which might provide a clue about the source or bleeding:

Facial or oral telangiectasia can suggest hereditary telangiectasia. Acanthosis nigricans in axilla suggest possible malignancy.

Perioral pigment spots are associated with Peutz-Jeghers syndrome. Purpura or ecchymosis implies possible bleeding disorder.

False positive FOB can result from pseudoperoxidase in various foods e.g. red meat, raw broccoli, turnips, cauliflower, radishes. A sensitive, quantitative measure is estimation of faecal concentration of ^{51}Cr-labelled RBCs.

Table 22: Causes of acute diarrhea

• Infections
Viruses (adenovirus, astrovirus, calicivirus (e.g. rotavirus, Norwalk agent), herpes simplex virus)
Bacteria (e.g. Campylobacter spp., C. difficile, E. coli, Salmonella enteritidis, Shigella spp.)
Parasites (e.g. E. histolytica, Giardia)
• Food poisoning/toxins
Bacillus cereus
Salmonella spp.
Staphylococcus spp.
Vibrio spp.
• Drugs
Antibiotics (e.g. amoxicillin)
Antihypertensives (e.g. angiotensin converting enzyme inhibitors)
Antineoplastic drugs
Digoxin
Antidepressants (e.g. Fluoxetine, lithium)
CNS drugs (e.g. L-dopa, valproic acid)
Cholesterol lowering drugs
GI drugs (e.g. magnesium containing antacids, prostaglandin analogues, H2- antagonists, sulphasalazine, prokinetic drugs)
Others: Theophylline, diuretics, oral hypoglycemic drugs, thyroxine, colchicine
• Poorly absorbed sugars: Fructose, mannitol, sorbitol
• Faecal impaction
• Intestinal ischemia

15. DIARRHOEA

Diarrhoea is decrease in consistency or increase in liquidity of stools.

Diarrhoea may be further defined as acute if <2 weeks, persistent if 2–4 weeks and chronic if >4 weeks in duration.

ACUTE DIARRHOEA

Table 22 enumerates causes of acute diarrhoea.

Chronic Diarrhoea

Table 23 enumerates causes of chronic diarrhea.

Eosinophilic gastroenteritis is a non-parasitic inflammatory disease of GI tract with various degrees of eosinophilic infiltration in tubular intestinal tract and biliary tree in absence of vasculitis or significant extraintestinal tissue eosinophilia.

Investigations for assessment of acute diarrhoea

- Spot stool specimen
  - Occult blood
  - Leucocytes
  - Ova, cysts and parasites
  - Culture and sensitivity
  - Giardia antigen
  - Clostridium difficile toxin
  - DNA probes
- Blood tests
  - Full blood count and differential
  - Urea and electrolytes
  - ESR and C-reactive protein
  - Blood culture
- Rigid sigmoidoscopy and biopsy
- Plain abdominal radiograph
- Flexible sigmoidoscopy
- Duodenal aspirates

Table 23: Causes of chronic diarrhea

• Dietary factors
Excess ingestion of fructose, sorbitol, caffeine
• Infections
Giardia lamblia
E. histolytica
Campylobacter enteritidis
Various organisms in immunocompromised (e.g. AIDS)
• Drugs
Antacids (magnesium trisilicate)
Antihypertensives (methyldopa, propranolol)
Theophylline
Frusemide
Methotrexate
Antibiotics (Amoxicillin, lincomycin)
Digoxin
Iron preparations
NSAIDs
• Lactose intolerance
• Malabsorption
Chronic pancreatitis
Bacterial overgrowth
Short bowel syndrome
• Inflammatory bowel disease
• Radiation colitis
• Neoplasms
Pancreatic cancer
Neuroendocrine tumours (carcinoid, gastrinoma), vasoactive intestinal polypeptide secreting tumour, medullary carcinoma of thyroid).
• Idiopathic secretory diarrhoea
Microscopic colitis
Collagenous colitis
Idiopathic bile salt diarrhoea
Post-cholecystectomy
Large - volume nonspecific secretory diarrhoea
• Endocrine disorders
Diabetes mellitus
Hyperthyroidism
Hypoadrenalism
• Functional bowel disorder
Purgative use and abuse
• Faecal incontinence
Autonomic neuropathy (e.g. diabetes)
Anorectal surgery
Latrogenic sphincter damage

MANAGING A CASE OF CHRONIC DIARRHOEA

History, Symptoms and Signs

1. History – (a) *Age*—Early life—Parasitic, dysentery, abdominal tuberculosis, genetic or biochemical abnormalities. Middle life—Colonic carcinoma, inflammatory bowel disease, pancreatic disease, laxative abuse. (b) *History of allergy.* (c) *Family history*—In hereditary pancreatitis, multiple neoplasia with multiple carcinoma of thyroid.
2. symptoms –
   (a) *Type of diarrhoea*—(i) *Size of stool*—Large stool (with little mucus) suggests small bowel disease. Small stool (with usually excess mucus) suggests large bowel involvement. (ii) *Constipation alternating with diarrhoea*—Carcinoma of colon, irritable bowel syndrome, diverticulosis, laxative habit, intestinal tuberculosis. (iii) *Relation to ingestion of food*—If of gastric origin diarrhoea immediately after each meal. Diarrhoea recurring after certain foods suggests allergy. (iv) *Time of day*—Urgent desire to evacuate in morning common in steatorrhoea. Nocturnal diarrhoea suggests presence of organic disease.
   (b) *Chronic bloody diarrhoea with systemic upset* is probably caused by ulcerative colitis, colonic Crohn's disease or infectious colitis (e.g. amoebic or bacillary dysentery). Less commonly ischemic colitis, radiation colitis or gut vasculitis (e.g. Behcet's disease, SLE, polyarteritis nodosa).
   (c) *Weight loss*—Diarrhoea associated with anorexia and weight loss suggests significant organic disease. Diarrhoea for many years without significant weight loss or systemic upset suggests irritable bowel syndrome. Diarrhoea with weight loss in spite of good appetite suggests thyrotoxicosis.
   (d) *Abdominal pain*—Colicky lower abdominal pain associated with bouts of diarrhoea may suggest colonic obstruction or diverticulitis. Abdominal pain with fatty diarrhoea in recurrent pancreatitis, tuberculosis or Crohn's disease.
   (e) *Abdominal distension*—Malignant disease, Crohn's disease, intestinal tuberculosis, or irritable bowel syndrome.
   (f) *Rectal tenesmus*—Cause in rectum or lower sigmoid. Also in ulcerative colitis or diverticulitis.
   (g) *Sense of urgency*—To pass frequent, small stools, that may be formed, loose or even pellety in irritable bowel syndrome.

3. Signs –
   (a) *Abdominal tenderness*—Diffuse in intestinal tuberculosis, over colon with diffuse colonic lesion.
   (b) *Doughy feel*—With abdominal tuberculosis.
   (c) *Abdominal bruit*—May be heard with stenosis of superior mesenteric artery.
   (d) *Mass*—Carcinoma, tumour or diverticulitis.
   (e) *Anal abnormalities*—Fissures, perianal or ischiorectal abscesses and fistulae may present as a complication of ulcerative colitis or Crohn's disease.
4. Type of faeces –
   1. *Mucus and blood*—Amoebic and bacillary dysenteries.
   2. *Profuse purulent discharge*—Chronic ulcerative colitis.
   3. *Mucus*—Irritable bowel syndrome, chronic constipation, following ingestion of strong purgatives, rarely in ulcerative colitis.
   4. *Fatty stools*—Voluminous, pale pasty stools in steatorrhoea.
   5. *Frequent soft, non-fatty stools*—Diarrhoea of gastric origin.
   6. *Large fermentative stools*—Sprue, nutritional deficiency states, fungus infections, intestinal carbohydrate dyspepsia.
   7. *With excessive bile*—Gastrointestinal hypermotility induced by vigorous purgatives or after severe gastro-enteritis, fistula between biliary tract and alimentary canal in a patient who has suffered from biliary colic attacks.
   8. *Watery stools*—Emotional diarrhoea, internal fistulae, reflex diarrhoea, extensive Crohn's disease, ulcerative colitis. In carcinoid syn. the secretory diarrhoea is profuse.

Differentiation of small bowel from large bowel diarrhoea is given in Table 24.

Table 24: Differentiation of small bowel from large bowel diarrhoea

Feature	*Small bowel diarrhoea*	*Large bowel diarrhoea*
Timing of diarrhoea	Any time	Usually on getting up in morning
Frequency of stools	Increased frequency of small stools	Normal to increased frequency of large stools
Pain if any	Central abdominal, not relieved by defecation	Often in left iliac fossa, relieved by defecation
Stool	Watery, or pale, fatty and offensive	With mucus or fresh blood, or watery

Investigations

Tests used in assessment of chronic diarrhoea

Initial Evaluation

Spot stool examination

- Gross characteristics
- Faecal occult blood
- Methylene blue stain for leucocytes
- Sudan stain for fat
- Microscopy for ova, cysts and parasites
- Culture and sensitivity

Quantitative stool collection

- 3-day stool weight/volume

Blood tests

- FBC and differential
- Urea and electrolytes, liver biochemistry, calcium and phosphate
- ESR, C-reactive protein
- Thyroxine and TSH
- Antigliadin, endomysial and reticulum antibodies
- Amoebic serology

Rigid sigmoidoscopy and biopsy

Further Evaluation

Spot stool examination

- Laxative screen
- *Giardia* antigen
- Acid-fast stain
- Faecal elastase
- Faecal chymotrypsin
- Sulphate/phosphate/magnesium concentration

Quantitative stool collection on 100 g/fat/day

Blood tests

- Haematinics
- INR
- Immunoglobulin
- Fasting 9 a.m. cortisol
- Fasting gut hormones

Urine

- Alkalinization
- Laxative screen 24-hour 5-hydroxyindole acetic acid
- 24-hour catecholamines
- Urinary indicans

Flexible sigmoidoscopy and biopsies
Gastroscopy and duodenal biopsies
Imaging
- Barium meal and follow-through
- Small bowel enema
- Abdominopelvic ultrasonography
- Barium enema
- CT of abdomen and pelvis

Breath tests
- Lactose hydrogen breath tests
- Glucose hydrogen breath test
- 14C glycolic acid breath test

Others
- Anorectal physiology studies

Trial of empirical treatment
- Restrictive diets (low-fat, lactose-free) (avoiding lactose for lactase deficiency or gluten for celiac sprue)
- Metronidazole
- Cholestyramine
- Pancreatic enzyme supplements
- Octreotide

Clonidine, an 2-adrenergic agonist, may allow control of diabetic diarrhoea

16. CONSTIPATION

Constipation can be defined as infrequent or difficult passage of faeces. It can also refer to hardness of stools or feeling of incomplete evacuation. Table 25 lists various causes of constipation.

Table 25: Causes of constipation

Gastrointestinal	*Non-GI disease*
Dietary	*Medications*
Insufficient fibre	Antacids containing aluminium or calcium
Obstruction	Tricyclic antidepressants
Tumours	Diuretics
Inflammation	Analgesics: Opioids, NSAIDs
Ischemia	Calcium channel blockers: Verapamil
Diverticular disease	Antipsychotics: Risperidone
Congenital abnormality (e.g. Hirschsprung's disease)	Anticholinergic: Belladona alkaloids
Motility disturbance	Antiparkinsonian drugs: Amantadine
Irritable bowel disease	*Metabolic/endocrine*
Hirschsprung's disease	Diabetes mellitus
Anorectal disease	Hypothyroidism
Crohn's disease	Hypercalcemia
Anal fissures	Pregnancy
Haemorrhoids	*Neurological*
Disorders of rectal evacuation	Spinal or pelvic nerve injury
Pelvic floor dysfunction	Cerebrovascular accident
Anismus	Parkinsonism
Descending perineum syndrome	Multiple sclerosis
Rectal mucosal prolapse	*Gynaecological: Pregnancy, ovarian cancer*
Rectocele	*Psychiatric disorders*
	Depression

HISTORY

1. Determine number of stools per week and duration of the problem. Ask about straining, pain, pressure and sense of obstruction to defecation, also consistency of stools. Note any associated complaints like abdominal pain and its location, bloating, gas and audible bowel sounds.
2. Any symptoms that might indicate an underlying disorder (secondary constipation).
3. Dietary and habitual fluid intake.
4. An acute or subacute onset of constipation should raise possibility of mechanical obstruction. In female patients the number and type and difficulty of deliveries since rectocoele and pelvic problems can be associated with constipation.

PHYSICAL EXAMINATION

- Abdominal size and girth
- Abdominal tenderness—Local or general
- Organomegaly
- Masses, including palpable left colon
- Perianal examination for excoriations, fissures and haemorrhoids
- Internal rectal examination—masses, gross or occult blood
- Ask the patient strain to expel the index finger during a digital rectal examination. Motion of the puborectalis posteriorly during straining indicates proper coordination of the pelvic floor muscles.
- Clinical examination to identify signs of an underlying medical illness, e.g. hypothyroidism.

INVESTIGATIONS

Barium enema: To exclude obstruction if constipation of recent onset.

Water-soluble contrast media: If megarectum or megacolon is suspected.

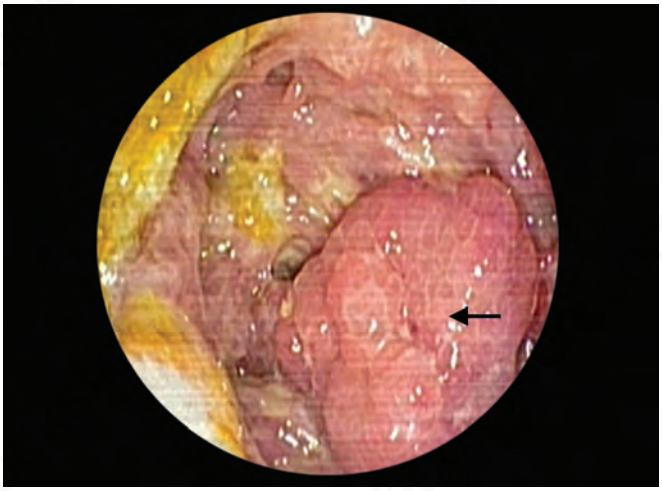


Fig. 23: Colonic growth

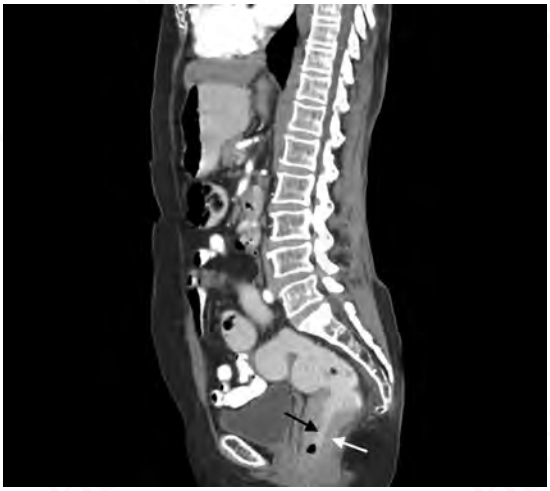


Fig. 24: Carcinoma of rectum: CECT showing narrowing of rectal canal due to mass

Flexible sigmoidoscopy plus barium enema or colonoscopy alone: Particularly in patients >40 years, to exclude structural diseases such as cancer or strictures (Fig. 23). Colonoscopy alone is most cost-effective in this setting because it provides an opportunity to biopsy mucosal lesions, perform polypectomy or dilate strictures.

Anorectal physiological studies to elicit anorectal inhibitory reflex and to exclude Hirschsprung's disease to assess pelvic floor coordination.

Upper gut barium studies: To exclude pseudo-obstruction if lower bowel is dilated.

Upper gut transit studies: if patient has upper gut symptoms or surgery for constipation is contemplated.

Proctography if a large rectocoele is suspected.

Abdominal CT scan: This can identify even small masses and delineate the extent of spread and metastasis (Fig. 24).

Balloon expulsion test: A balloon-tipped urinary catheter is placed and inflated with 50 mL of water. Normally, a patient can expel it while seated on a toilet or in the left lateral decubitus position. In the lateral position, the weight needed to facilitate expulsion of the balloon is determined; normally, expulsion occurs with <200 g added

If positive, an anatomic evaluation of the rectum or anal sphincters and an assessment of pelvic floor relaxation are done.

MANAGEMENT

- Increase in dietary fibre, bulking agents such as isabgol and laxatives. If continued use of laxatives is unavoidable, rectal stimulants e.g. glycerine or bisacodyl suppository, or oral senna preparation or oral bisacodyl. 5-HT4 (serotonin[4]) agonists may have a role initiating peristalsis when laxatives have failed or are poorly tolerated.
- Behavioural techniques—Such as 'biofeedback' and bowel retraining in those with abnormal pelvic floor coordination.
- Surgery—Subtotal colectomy or ileorectal anastomosis as a last resort, but results unpredictable.

Idiopathic megarectum and megacolon—Symptoms may be present from birth, childhood or adulthood. Aetiology is unknown.

Hirschsprung's disease has variable pattern of inheritance and the major susceptibility gene is *RET* proto-oncogene. It should be excluded by contrast studies of the large bowel, elicitation of the recto-anal inhibitory reflex or full-thickness rectal biopsy taken 2 cm above dentate line.

Management—(a) Faecal disimpaction using enemas. Life-long laxatives may be required. (b) Behavioural therapy can improve defecatory behaviour in some. (c) Colectomy with ileorectal anastomosis achieves a normal bowel frequency in 80%.

17. MALABSORPTION

Malabsorption is a failure of normal absorption of nutrients. Principal types of malabsorption are generalized and specific.

Generalized malabsorption affects all classes of nutrients. It usually results from small intestinal disease

or conditions in other organs (Table 26). When severe, it is manifested by one or more clinical features of malabsorptive stage. Because fat absorption is most affected, excess undigested fat in the stool (steatorrhoea) is strong evidence of generalized malabsorption.

Specific malabsorption is a failure of the processes governing absorption of one class or type of nutrients, e.g. genetic or acquired failure to absorb disaccharide sugars (e.g. lactase or vitamin B_{12} deficiency).

HISTORY

- Diarrhoea and weight loss
- Family history may suggest coeliac disease, Crohn's disease or familial pancreatitis
- Previous surgery may lead to short gut syndrome or create other abnormalities predisposing to bacterial overgrowth
- Immunodeficiency may lead to frequent infections
- Radiation treatment may cause radiation enteritis
- Obvious heavy steatorrhoea (oily stools) may indicate pancreatic insufficiency
- Abdominal pain though uncommon, suggests a diagnosis of pancreatitis, intestinal strictures or small intestinal ischemia

INVESTIGATIONS

Blood Tests

Tests for Evidence of Malabsorption

- Full blood count
- Mean cell volume, mean corpuscular hemoglobin
- Serum iron/total iron-binding capacity (or ferritin)
- Vitamin B_{12}
- Serum (or RBC) folate
- Prothrombin time
- Plasma proteins

Table 26: Causes of generalized malabsorption

I. Conditions within gut lumen
A. Defective substrate hydrolysis
• Pancreatic enzyme deficiency
– Chronic pancreatitis
– Cystic fibrosis
– Cancer of pancreas
– Z-E syndrome
– Hypothyroidism (also villous atrophy)
• Enzyme inactivation
– Z-E syndrome
Contd...
Contd...
• Intestinal hurry
– Gastroenterostomy
– Postgastrectomy
– Thyrotoxicosis
B. Lack of solubilising bile salts
(failure of micelle formation)
• Reduced bile salt synthesis
– Parenchymal liver disease
– Cholestatic jaundice
• Bile salt deconjugation
– Z-E syndrome
– Bacterial over growth
• Increased faecal loss of bile salts
– Terminal ileal disease
– Tuberculosis
– Crohn's disease
C. Deficiency of certain factors
• Achlorhydria
• Lack of intrinsic factor
– Pernicious anaemia
• Increased consumption of Vit. B_{12} in intestine
– Blind loop or stagnant loop syndrome
D. Immunological
• Immunoproliferative small intestinal disease (IPSID)
E. Drugs (Refer to Drug-induced GI disease)
II. Conditions in gut mucosa
(Reduced absorptive area)
• Normal mucosa
– Lactase difficile
• Abnormal mucosa
– Coeliac disease
– Tropical sprue
– Giardiasis
– Whipple's disease
– AIDS
III. Disorders of transport from mucosal cell
• Lymphatic obstruction
– Tuberculosis
– Lymphangiectasia
– Lymphoma (abdominal)
• Epithelial processing defect
– Abetalipoproteinemia
IV. Systemic diseases
Thyrotoxicosis
Hypothyroidism
Diabetes mellitus
Collagen vascular diseases
Addison's disease
Note: Tropical sprue continues to be the commonest cause following coeliac and Crohn's disease.

Tests for Cause of Malabsorption

- C-reactive protein, ESR
- Immunoglobulins (hypogammaglobulinemia)
- Endomysial and antigliadin antibodies (coeliac disease).

Small intestinal biopsy at endoscopy with punch biopsy forceps. Normal histology with well-formed villous pattern almost excludes diffuse intestinal mucosal disease. In difficult cases, endoscopic small intestinal biopsy may provide information, and allows dissecting microscopic appearance to be examined readily.

Capsule endoscopy as alternative to biopsy of small intestine to detect villous atrophy in patients suspected of coeliac disease.

- Total or subtotal villous atrophy in coeliac disease.
- Mucosal lesions or trophozoites in mucus layer in giardiasis.
- Lipid-filled vacuoles distending villous epithelium in Abetalipoproteinemia.
- PAS positive engorged macrophages filling lamina propria and dilated vacuoles in Whipple's disease.
- Other diseases—Diffuse small bowel Crohn's disease, intestinal lymphangiectasia, diffuse intestinal lymphoma, and various allergic gastroenteropathies (e.g. soya protein intolerance) can also be diagnosed.

Radiology

Barium Meal Follow-through

- Delayed transit time
- Abnormal small intestinal pattern:

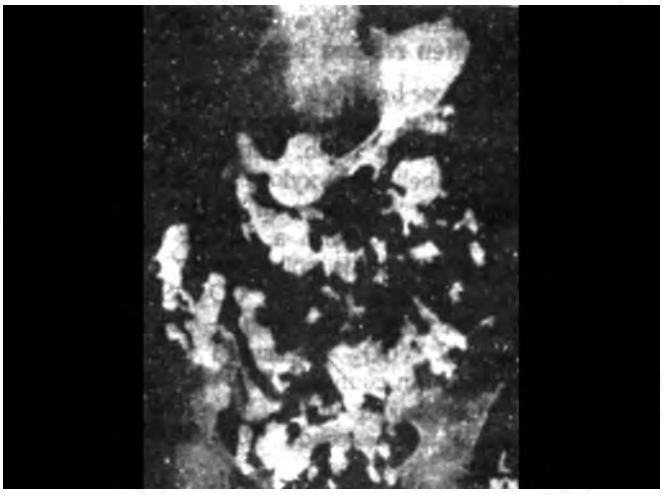


Fig. 25: Fragmentation and clumping of barium in the small intestine indicating malabsorption

(a) Smooth appearance of margins of barium-filled intestine.
(b) Clumping of barium (Fig. 25) or transformation of a normal feathery appearance to a ladder pattern resembling a stack of coins.
(c) Radiological anatomical abnormality in stagnant loop syndromes, small intestinal resection, Crohn's disease, systemic sclerosis.
(d) Nodular lymphoid hyperplasia suggests immunoglobulin deficiency and possibility of an enteric infection such as giardiasis. In older individuals radiology may reveal multiple diverticulae leading to bacterial overgrowth.

PHYSICAL FINDINGS

Physical findings in malabsorption are related to malabsorption of specific nutrients (Table 27).

Table 27: Physical findings in malabsorption

Malabsorbed nutrients	*Symptoms and signs*
Fat soluble vitamins	
Vitamin A	Hyperkeratosis
	Night blindness
Vitamin D	Osteomalacia
	Proximal myopathy
	Rickets in children
Vitamin K	Bruising
	Bleeding
Water soluble vitamins	
Vitamin B_1	Beriberi
	Fluid retention
	Brainstem lesions
	Ataxia
	Wernicke's encephalopathy
Niacin	Pellagra
	Dermatitis
	Diarrhoea
	Dementia
Vitamin C	Petechial hemorrhage
	Swollen gums
	Hyperkeratosis
	Follicular congestion
Folic acid	Glossitis
	Macrocytic anaemia

Contd...

Contd...

Haematinics	
Folic acid	Macrocytic anaemia
Vitamin B_{12}	SCD
Iron	Microcytic anaemia
	Koilonychia
Minerals	
Calcium	Paraesthesias
Magnesium	Tetany
Zinc	Acrodermatitis
	Poor wound healing
	Defective taste
Proteins	Muscle wasting
	Peripheral oedema
Bile salts	Watery diarrhoea

PANCREATIC DISEASE

- **Radiograph—**Pancreatic calcification
- **Ultrasonography—**(Calcification and complications, e.g. pseudocysts, duct dilatation)
- **CT—**(Calcification, gland atrophy, cysts and duct dilatation)
- **ERCP or MRI**

Investigations

Table 28 enumerates various absorption tests.

18. COELIAC DISEASE

In coeliac disease, the mucosa of small intestine is abnormal. The condition improves morphologically and symptomatically with a gluten-free diet and relapses

Table 28: Absorption Function tests

Test	*Method*	*Interpretation*
Carbohydrate malabsorption		
Hydrogen breath test	After overnight fast, basal samples taken and 50 g lactose in 200 mL in water. End-expiratory blood samples analysed at 15 or 30 min interval for 2 hours	If bacteria in upper gut, or lactose absent, increased excretion of H_2 in breath. Positive test is increase of 200 ppm or more
Fat malabsorption (Pancreatic function)		
Triolein test	Oral dose of labelled fat and measurement of $^{14}CO_2$ in expired breath	Tests ability to digest fat
3-day faecal fat collection	Adequate amount of fat intake (70 g/d)	Normal amount of fat in stool <5 g/day. More fat excretion confirms steatorrhoea.
Tubeless test	Pancreolauryl test links a fluoresceinated probe to a carrier by a link that is sensitive to pepsin	Low proportion of ingested dye recovered from urine when luminal trypsin is reduced in pancreatic insufficiency
N-benzoyl-tyrosyl paraamino-benzoic acid test	After fasting, oral dose of 500 mg NBT-PABA is given with 250 mL water	Normal subjects excrete more than 57% in 6 hours. Test relies on hydrolysis of NBT-PABA by trypsin and subsequent excretion of paraamino-benzoic acid and its metabolites.
Ileal function		
SeHCAT test scan	Patient's 7-day retention of oral dose of labelled bile acid (Se-homo-cholyltaurine) after whole body scan	Low (<7%) in extensive ileal disease or bile salt malabsorption.
Schilling test (Vitamin B_{12} absorption)	Ingestion of radioactive B_{12} and measurement of urinary recovery	If cause of abnormal B_{12} absorption is gastric, it can be corrected by co-administration of B_{12}, if cause is terminal ileum it cannot be corrected.
D-xylose absorption test	5 g D-xylose p.o. to fasting patient and urine collected at 30 min. intervals for next 5 hours.	An abnormal test (<4.5 g excretion) primarily reflects the presence of duodenal/jejunal mucosal disease, blind loop syndrome.
Tests of small bowel contamination	Aspiration Uncontaminated small bowel aspirate with pre-sterilized, sheathed aspiration cannula. Aerobic and anaerobic culture of aspirate	Total aerobic and anaerobic count of 105 or more suggests bacterial overgrowth.

Table 29: Presenting features of coeliac disease

• Diarrhoea (most common)	• Infertility, recurrent miscarriage
• Lassitude	• Severe anemia and/or unexplained diarrhoea in pregnancy
• Weight loss	• Mild microcytic anaemia with persistent low serum or RBC folate
• Osteomalacia	
• Aphthous ulceration	
• Glossitis	
• Myopathy	
• Skin complains (e.g. eczema)	

when gluten is re-introduced. It was previously called non-tropical sprue, idiopathic steatorrhoea or primary malabsorption.

CLINICAL FEATURES

Presenting features of coeliac disease are given in Table 29. Patients with coeliac disease are usually short, and 60% of children are below the third centile for age. Development of secondary sex characteristics is often delayed. Delayed eruption of teeth, finger clubbing and koilonychia may be seen and oedema and ascites occur occasionally in severe cases due to hypoproteinemia.

INVESTIGATIONS

Hematology—Mild hypochromic microcytic anemia. Blood film may show Howell-Jolly bodies, siderocytes, irregular and crenated RBCs, Heinz bodies, microspherocytes, acanthocytes and occasionally erythroblasts.

Laboratory tests—Patients with untreated coeliac disease have IgA antigliadin, IgA antiendomysial, and IgA anti-tTG antibodies. Elevated tTg antibody titres are 90–95% sensitivity and 90–95% specificity

Bone densitometry for osteoporosis.

Endoscopic small intestinal biopsy. Classical changes are villous flattening of small intestinal mucosal epithelium, inflammation of lamina propria, reduced epithelial surface cell height, increased intra-epithelial lymphocyte count.

Radiology—With barium follow-through or small bowel enema often reveals small intestinal segmentation, dilatation and loss of the normal, fine feathery pattern of the mucosa. CT and MRI may reveal small bowel dilatation with hyposplenism, and are useful in diagnosing complicating malignancy and caseating mesenteric lymph nodes.

MANAGEMENT

Diet—Gluten-free diet avoiding wheat, rye and barley products. Strict dietary restriction not only reduces the increased incidence of small intestinal T cell lymphoma, but also of autoimmune disorders including diabetes mellitus and thyroid disease. The diet is low in fibre, so regular addition of rice bran and ispaghula husks is useful. Specific dietary deficiencies (e.g. iron, folic acid, occasionally B_{12}) should be corrected.

Corticosteroids can control coeliac disease, leading to rapid cessation of diarrhoea, weight gain and improved fat absorption. However, symptoms usually return within a few days after stopping treatment. Corticosteroids should therefore be reserved for severe illness, a coeliac crisis or otherwise unresponsive disease.

Follow-up—After a gluten-free diet for 3–4 months, a repeat small intestinal biopsy should be taken to determine whether the mucosal morphology has improved. If there is no improvement, other causes of villous atrophy (e.g. giardiasis, cow's milk allergy, HIV infection) should be excluded.

TROPICAL SPRUE

It is a malabsorption disorder seen in tropical areas and is manifested by chronic diarrhoea, steatorrhea, weight loss and nutritional deficiencies including those of both folate and cobalamin.

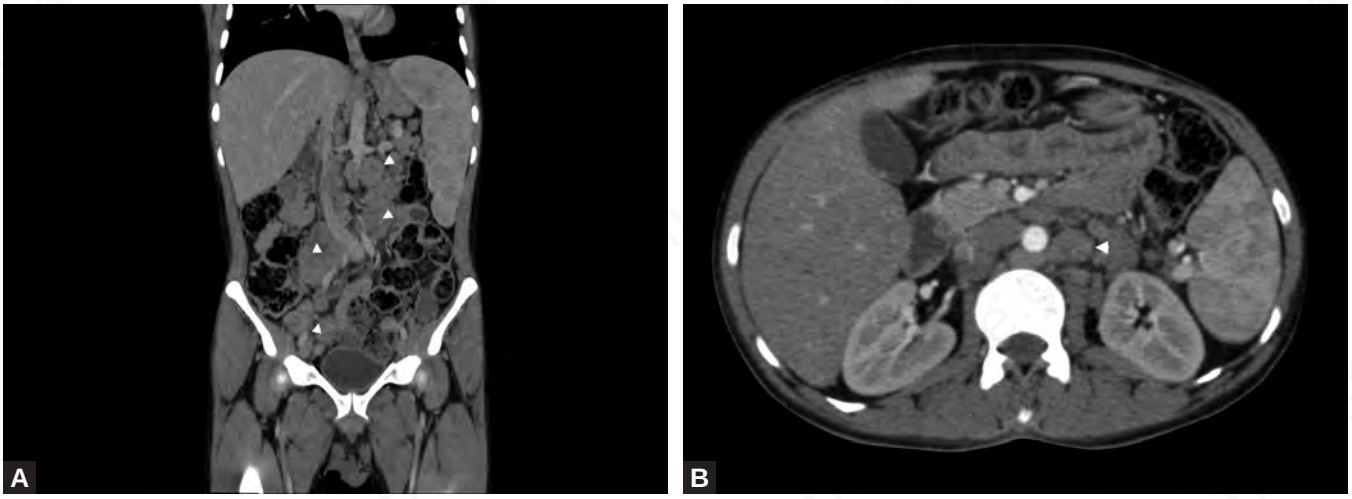
It is a diagnosis of exclusion as chronic diarrhea in a tropical environment is most often caused by infectious agents, including *G. lamblia, Yersinia enterocolitica, C. dfificile, Cryptosporidium parvum*.

Tropical sprue should not be entertained as a possible diagnosis until the presence of cysts and trophozoites has been excluded in three stool samples.

Its occurrence is not evenly distributed in all tropical areas, it is found in specific locations, like southern India, Philippines.

Aetiology—The aetiology and pathogenesis of tropical sprue are uncertain. As tropical sprue responds to antibiotics the consensus is that it may be caused by one or more infectious agents.

Klebsiella pneumonia, Enterobacter cloacae and E. coli have been implicated in some studies of tropical



Figs. 26A and B: Contrast CT abdomen showing lymphadenopathy (A) coronal view venous phase; (B) axial view arterial phase

sprue, while other studies have favoured a role for a toxin produced by one or more of these bacteria.

Diagnosis—The diagnosis of tropical sprue is best based on an abnormal small-intestinal mucosal biopsy in an individual with chronic diarrhoea and evidence of malabsorption who is either residing or has recently lived in a tropical country.

The small-intestinal biopsy in tropical sprue does not reveal pathognomonic features but resembles and can often be indistinguishable from, that seen in celiac disease.

The biopsy sample in tropical sprue has less villous architectural alteration and more mononuclear cell infiltrate in the lamina propria.

In contrast to those of celiac disease, the histologic features of tropical sprue manifest with a similar degree of severity throughout the small intestine and a gluten-free diet does not result in either clinical or histologic improvement in tropical sprue.

Treatment—Broad-spectrum antibiotics and folic acid are most often curative. Tetracycline should be used for up to 6 months and may be associated with improvement within 1–2 weeks. Folic acid alone induces hematologic remission as well as improvement in appetite, weight gain and some morphologic changes in small intestinal biopsy.

19. ABDOMINAL TUBERCULOSIS

Abdominal tuberculosis can affect the GI tract, peritoneum, lymphnodes of the small bowel mesentery (Figs. 26A and B), or solid viscera (liver, spleen, pancreas). The terminal ileum and ileocaecal region are the most common sites, possibly because of increased rate of fluid and electrolyte absorption, minimal digestive activity and abundance of lymphoid tissue followed by the jejunum and colon. Multiple sites are common.

Clinical features of abdominal tuberculosis are very variable as listed in Table 30.

Signs: Vigorous peristaltic activity or distended bowel may be noted. Tenderness usually in right lower quadrant. Muscle guarding if peritoneum is involved. In presence of ileocaecal tuberculosis a tender fixed mass may be palpated in half the cases.

DIAGNOSIS

1. ***Clinical***—Possibility of intestinal tuberculosis should be considered if – (i) Lung cavity with positive sputum. (ii) Abdominal symptoms appear in association with change of bowel habit. (iii) Temperature becomes irregular without change in lung lesion. (iv) Sudden reversal of pulmonary T.B. not explained by condition of lung lesion, or unsatisfactory clinical course in spite of adequate treatment.
2. ***Radiology***—Suggestive features on barium meal examination – (i) Lack of barium retention in diseased segment of ileum and/or caecum (Stierlin sign). (ii) Persistent narrow stream of barium in small bowel (String sign). (iii) Areas of small bowel obstruction manifested by dilatation and delay in emptying in association with short segments of irregularity of bowel silhouette (Fig. 27) and mucosal markings. (iv) Single filling defect in caecum in hypertrophic tuberculosis. (v) Broad-based triangular appearance of terminal inch of ileum with base towards caecum (Fleischner sign).

Table 30: Clinical features of abdominal tuberculosis

Site of involvement	*Type of lesion*	*Modes of presentation*	*Clinical features*
Small intestine	Ulcerative	Chronic	Diarrhoea, malabsorption, lower GI bleeding, fever. Acute int. perforation, peritonitis.
	Stricture	Acute on chronic	Acute on chronic int. obstruction
		Chronic	Subacute intestinal obstruction
		Acute	Acute int. obstruction
Ileocaecum and large intestine	Hypertrophic	Chronic	Mass, subacute int. obstruction
	Ulcero-hypertrophic	Acute on chronic	Acute on chronic int. obstruction
Peritoneum	Ascites	Acute	Acute int. obstruction
		Chronic	Lower GI bleeding, fever
	Adhesive	Chronic	Pain, ascites, fever Subacute int. obst.
		Acute	Acute TB peritonitis
		Acute-on-chronic	Acute-on-chronic int. obstruction
Liver	Diffuse hepatic involvement as in miliary TB. Single or multiple tuberculomas or abscesses.		

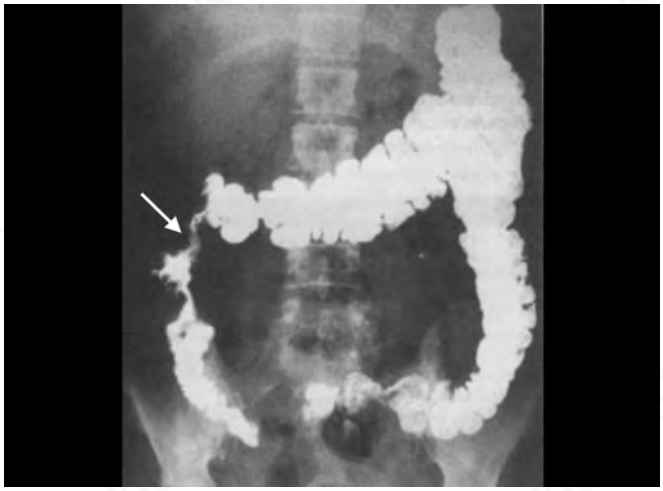


Fig. 27: Colonic stricture due to tuberculosis

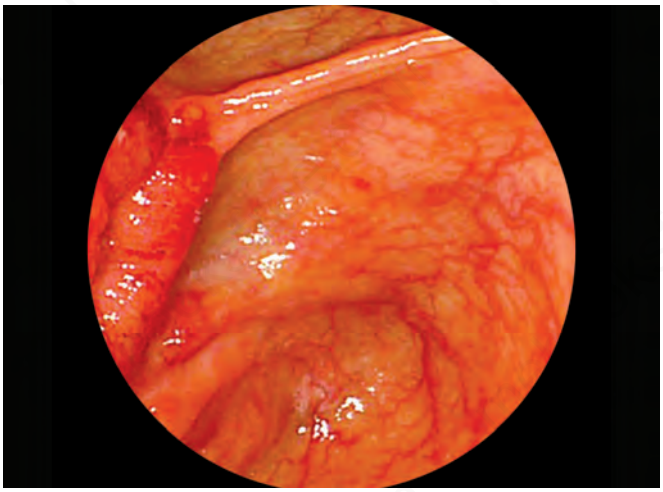


Fig. 28: Ileocaecal TB

3. ***Histology***—Demonstration of mycobacterium tuberculosis or histological evidence of tubercles with caseation necrosis tissues for histological examination can be obtained by – (a) Percutaneous fine-needle aspiration cytology (FNAC) from an abdominal mass, or ultra-sound guided or CT-guided FNAC from enlarged lymphnodes. (b) Colonoscopic biopsy from colonic and ileocaecal lesions (Fig. 28). (c) Laparoscopic biopsy of parietal peritoneum.

MANAGEMENT

1. Diet—Bland, low in residue. Low fat diet if steatorrhoea.
2. Anti-tuberculous therapy.
3. Fat soluble vitamins, Vitamin C and calcium.
4. Pancreatin 1–4 gm. after each meal if very poor absorption.
5. Surgery: Indications—(a) Localised tuberculous involvement of hyperplastic type with marked diminution of lumen caliber. (b) Stenosis of bowel causing obstruction. (c) Perforation of tuberculous ulcer.

20. IRRITABLE BOWEL SYNDROME

IBS consists of a group of GI symptoms particularly associated with lower bowel in absence of demonstrable organic pathology.

CRITERIA FOR IRRITABLE BOWEL SYNDROME (ROME CRITERIA)

Recurrent abdominal pain or discomfort for at least 3 days per month in last 3 months (with symptoms onset at least 6 months prior to diagnosis) associated with two or more of the following:

1. Improvement after defecation
2. Onset associated with change in frequency of stool
3. Onset associated with change in form (appearance) of stool

Other symptoms that are not essential but support the diagnosis of IBS:

- Abnormal stool frequency (>3 bowel movements/day or <3 bowel movements/week)
- Abnormal stool form (lumpy/hard or loose/watery stools)
- Abnormal stool passage (straining, urgency or feeling of incomplete bowel movement)
- Passage of mucus
- Bloating or feeling of abdominal distension

CLINICAL TYPES

1. Chronic abdominal pain with constipation
2. Diarrhoea predominant IBS
3. Mixed IBS: Alternating diarrhoea and constipation

AETIOLOGY

1. ***Pathophysiology***
   (a) **Disturbance of GI motility**—In IBS, the fasted small intestine shows subtle differences in activity, particularly under conditions of stress and during sleep.
   (b) **Sensory abnormalities (visceral hyperalgesia).** IBS patients report discomfort at lower volume of gut distension. Such patients may suffer from 'visceral hypersensitivity' and the cause of the problem may be neural abnormality of the primary afferent nerves to the spinal cord, or of the intrinsic nerves of the colonic wall.
2. ***Psychopathology***—Patients in whom continuous pain is the major symptom suffer more from depressive symptoms, whereas those with chronic unremitting symptoms tend to have subtle personality differences and low self-esteem. Marital difficulties and childhood physical abuse are reported more commonly in chronic IBS patients.
3. ***Post-infective/post-inflammatory causes***—Onset of symptoms may follow an enteric infective episode (e.g. Campylobacter), and IBS-like symptoms are common in patients with coexistent inflammatory bowel disease.
4. ***Abnormal regulatory physiology—***Patients with IBS have been reported to exhibit exaggerated GI responses, either as intrinsic reflexes (e.g. motility response to eating or infused cholecystokinin) or to exogenously infused drugs (e.g. cholinergics) and the stress-response mediator corticotrophin-releasing hormone (CRH).
5. ***Diet***—Colonic fibre fermentation may be a source of perceived excess gas, and has led to suggestions of a role of abnormal colonic bacterial flora.

DIAGNOSIS

- Full blood count, ESR and sigmoidoscopy in patient under 40 with classical history of IBS and without significant disturbance or significant weight loss.
- Double-contrast barium enema or colonoscopy in patients over 40 with recent onset of symptoms to rule out malignancy.
- Rectal biopsy in patients with diarrhoea. Changes of inflammatory bowel disease or less common types of colitis may be found in a macroscopically normal rectum.
- In patients with chronic diarrhoea, further investigations to rule out coeliac disease, Crohn's disease and chronic GI infection e.g. giardiasis.

MANAGEMENT

1. ***Explanation and reassurance***—Physiological explanation based on concept of 'spasm' of bowel. Reaction of the gut can be equated to reaction to emotion e.g. fast pulse and dry mouth to apprehension. Reassurance regarding absence of organic disease.
2. ***Specific therapy***—According to the predominant complain of the patient.

Dietary Measures

Dietary fibre—With supplementation with bulking agents such as coarse wheat bran or ispaghula husk in gradually increasing amount.

Exclusion diets—Lactose-free diets may be tried in individuals with unexplained, chronic, painless diarrhoea.

Drug Therapy

Antispasmodics—Mebeverine 100 mg or Pinaverium bromide 50 mg, 30 minutes before food if symptoms following meals.

Antidiarrhoeal agents—Loperamide, codeine (long-term use may produce addiction) or diphenoxylate, if frequent loose stools.

Antidepressants—In patients with anxiety provoked symptoms.

Tegaserod—5 mg b.d. ½ hour before food if associated constipation predominant IBS.

Lubiprostone—Stimulates chloride channels in the apical membrane of intestinal epithelial cells. Chloride secretion induces passive movement of sodium and water into the bowel lumen and improves bowel function. Oral lubiprostone was effective in the treatment of patients with constipation-predominant IBS.

Linaclotide—It is a minimally absorbed 14-amino-acid peptide guanylate cyclase-C (GC-C) agonist that binds to and activates GC-C on the luminal surface of intestinal epithelium. Activation of GC-C results in generation of cyclic guanosine monophosphate (cGMP), which triggers secretion of fluid, sodium and bicarbonate. The analgesic action of linaclotide appears to be mediated by cGMP acting on afferent pain fibers innervating the GI tract. The drug has been approved for treatment of constipation in IBS-C patients. 290 μg given once daily, significantly improved abdominal pain, bloating and spontaneous bowel movement.

3. ***Non-drug treatment***—If no response to conventional therapy. (a) Elimination diets when diarrhoea is predominant symptom in a well-motivated subject. (b) Relaxation techniques for stress management. (c) Specific biofeedback. (d) Psychotherapy. (e) Hypnotherapy.

21. DIVERTICULAR DISEASE

The term *Diverticulosis* simply describes the presence of diverticula. *Diverticulitis* is the clinical syndrome resulting from inflammation of a diverticulum.

Diverticular colitis—Mucosal changes are thought to be an idiosyncratic inflammatory response to diverticulitis.

AETIOLOGY

1. More common in older individuals. 2. Eating habits – Diverticulosis is less common in vegetarians than those who eat meat. Hence a diet poor in fibre is associated. 3. Factors that lead to constipation and colonic hypermotility or to a weak colonic wall may be involved.

PATHOGENESIS

Colonic diverticula are pulsion diverticula; they arise when the pressure within the colon is excessive and the wall is weakened as a result of ageing. The sigmoid colon is the most common site for diverticulae formation. Occasionally the descending colon, less commonly the whole colon is involved. *Diverticulitis* occurs when a diverticulum becomes irritated by inspissated faecal material (faecolith).

COURSE OF THE DISEASE

1. **Uncomplicated diverticular disease**—No symptoms unless the wall changes are so severe as to cause obstruction.
2. **Rectal bleeding** is uncommon but tends to be sudden and profuse. Such bleeding usually occurs in simple diverticulosis rather than diverticulitis.
3. **Diverticulitis and pericolitis** are usually associated with pain and tenderness in right iliac fossa that starts suddenly. Right-sided disease can mimic acute appendicitis. Patient may become extremely ill with peritonitis or Gram-negative septicaemia.
4. **Pericolic abscess** may occur in or outside the wall. Symptoms can be vague (e.g. anorexia, weakness). Abdominal and pelvic examination can reveal a tender mass.
5. **Fistulas**—An untreated pericolic abscess can erode into a neighbouring hollow organ, producing a fistula. Fistulas can cause new symptoms (e.g. pneumaturia and repeated urinary infections in case of colovesical fistula, malabsorption in colojejunal fistula). In women colovaginal fistulas are more common in women who have undergone hysterectomy.

INVESTIGATIONS

- *Barium enema.* Diverticulosis is readily detected. Barium enema and colonoscopy avoided in acute condition due to risk of perforation during procedure.
- *Abdominal CT* is also effective for diagnosis.
- *Colonoscopy* if chronic bleeding or insidious change in bowel habit, symptoms which may be caused by cancer of sigmoid colon which can be overlooked on barium enema in presence of diverticular disease. Colonoscopy should be performed after 6 weeks after attack of diverticular disease.

MANAGEMENT

1. **Symptomatic, uncomplicated diverticular disease**—Treatment same as irritable bowel syndrome. High fibre diet and/or bulking agents such as ispaghula and bran. If diarrhoea is the main symptom, antidiarrhoeal drugs. Musculotropic drug like mebeverine may relieve pain. Psychological support if anxiety or depression.

2. **Rectal bleeding**—Transfusion may be required in elderly patients. Occasionally embolization of bleeding vessel best performed at time of angiography.
   Endoscopic hemostasis by adrenaline injection.
3. **Diverticulitis and pericolitis**—Hospitalization with rest and analgesics, nil by mouth and antibiotics against aerobic and anaerobic bacteria (e.g. cefuroxime and metronidazole).
4. **Pericolic abscess and fistulas**—CT and ultrasound imaging techniques allow abscesses to be drained percutaneously. Fistulas require surgery.

22. INFLAMMATORY BOWEL DISEASE

ULCERATIVE COLITIS (UC)

Ulcerative colitis is an inflammatory disorder of the colonic mucosa characterized by relapses and remissions. The rectal mucosa is always involved, occasionally by microscopic inflammation alone, and the disease extends proximally.

UC is classified into severity in two ways—According to extent of involvement or according to symptoms. If the disease is limited to only the rectum (proctitis), limited to rectum and sigmoid colon (proctosigmoiditis). Left sided UC involves descending colon, sigmoid colon and rectum. The term pancolitis suggests involvement of the whole colon or most of the colon. Sometimes ileum gets involved called as "Backwash ileitis".

Potential etiological factors in UC are listed in Table 31.

Clinical Features

Presentation—Onset is usually gradual. Bloody diarrhoea is the hallmark of the disease, though proctitis may present with rectal bleeding and constipation. Urgency and crampy abdominal discomfort before defecation. Stool frequency is related to the severity of the disease. Assessment of the severity of disease is given in Table 32.

Systemic features and signs—Anorexia, weight loss. Anemia, fever, tachycardia, abdominal tenderness.

Extra-intestinal Manifestations

Ulcerative colitis has very varied systemic manifestations as given in Table 33.

Investigations

Sigmoidoscopy and rectal biopsy—The appearances can be graded as – (a) Mild: Hyperaemia and oedema. (b) Moderate: Granular mucosa with contact bleeding. (c) Severe: Ulceration, spontaneous bleeding.

Table 32: Assessment of severity

Features	*Mild*	*Moderate*	*Severe*
Motions per day	< 4	4 to 6	> 6
Rectal bleeding	Little	Moderate	Large quantities
Fever	None	Mild	> 37.8ºC on 2 of 4 days
Pulse rate	Normal	Intermediate	> 90 beats/min.
Hemoglobin	Normal	> 10.5 g/dL	< 10.5 g/dL
ESR	Normal	Slight rise	> 30 mm/hr.
Endoscopic appearace	Erythema, decreased vascular pattern, fine granularity	Marked erythema, coarse granularity, absent vascular markings, contact bleeding, no ulcerations	Spontaneous bleeding, ulcerations

Table 31: Potential etiological factors in UC

Factors	*Evidence*
Genetic	1:10 to 1:15
• Family frequency	70% of affected sib pairs suffer
• Concordance	
• HLA	Association with panocolitis
• Chromosomes 12, 6 and 2	Microsatellite markers
Psychological	Major stress can cause flarecup or precipitation of symptoms
Immunological	
• 40kDA colonic protein	Tumor necrosis factor
• Cellular mechanisms	
• Cytokines	
• Neuroimmune	
Environmental	
• Sulphate-reducing bacteria	
• Smoking	Excess hydrogen sulphide
• Appendicectomy	Protects—Ex-smokers at most risk
• Anti-inflammatory drugs	Protects
• Dietary factors	70% before UC
	Deficiency or excess of certain nutrients (1-arginine, gluten)

Table 33: Systemic manifestations of ulcerative colitis

Related to activity	
Common	*Uncommon*
Aphthous ulcers	Pyoderma gangrenosum
Erythema nodosum	Thromboembolism
Episcleritis	
Arthritis (large joints)	
Unrelated to activity	
Common	*Uncommon*
Sacroiliitis	Primary sclerosing cholangitis
Arthralgia	Other liver disease
(small joints)	Ankylosing spondylitis Sweet's syndrome

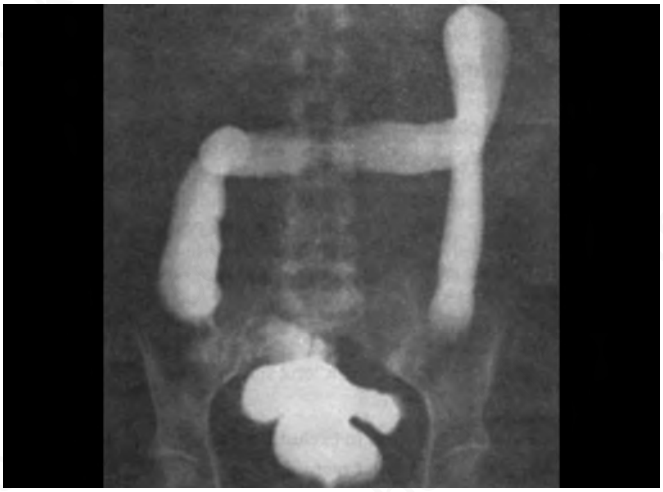


Fig. 29: Barium enema showing marked contraction and shortening of the colon (pipe stem appearance) due to long-standing ulcerative colitis

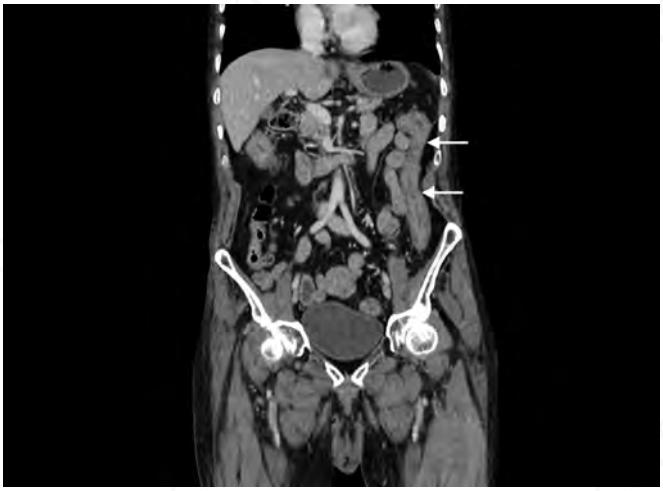


Fig. 31: Descending colitis

Characteristic microscopic features are a chronic inflammatory infiltrate, glandular distortion, goblet cell depletion and crypt abscesses. The crypt architecture of the colon is distorted; crypts may be bifid and reduced in number, often with a gap between the crypt bases and the muscularis mucosae.

Some patients have basal plasma cells and multiple basal lymphoid aggregates.

Ileal changes in patients with backwash ileitis include villous atrophy and crypt regeneration with increased inflammation, increased neutrophil and mononuclear inflammation in the lamina propria and patchy cryptitis and crypt abscesses.

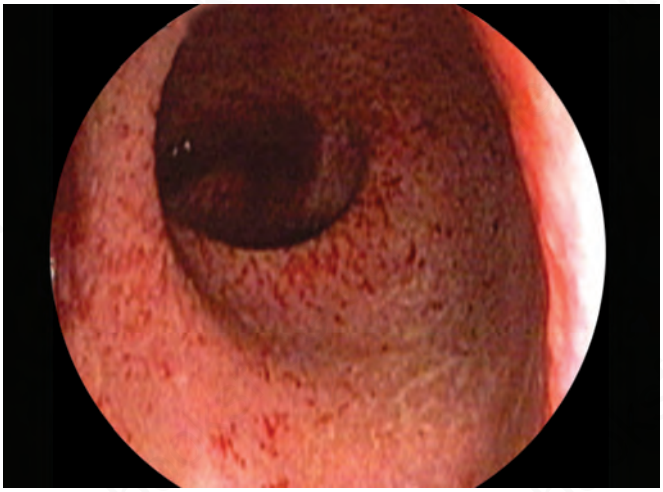


Fig. 30: Colonoscopy in active ulcerative colitis

Plain abdominal radiography in only severe disease, to assess faecal distribution (the distal extent identifies the proximal extent of colitis in majority of patients), to exclude colonic dilatation (> 5.5 cm). It is also helpful in demonstrating proximal constipation in patients with very distal disease.

Colonoscopy vs barium enema—Typical barium enema features are as shown in Figure 29. Colonoscopy is always preferable in initial investigation of bloody diarrhoea, because it provides better mucosal definition and allows biopsies (Fig. 30). Colonoscopy however is dangerous in acute episode; flexible sigmoidoscopy after phosphate enema is then the procedure of choice.

CT abdomen can also define active colitis (Fig. 31) and its proximal extent.

Other investigations

Stool examination to exclude pathogens such as *E. histolytica, Clostridium difficile, E. coli, Campylobacter* spp. and *Shigella* spp.

Full blood count, ESR or C-reactive protein to evaluate severity.

Liver function investigation once in remission.

Differential Diagnosis

Infection—Other causes of bloody diarrhoea include Clostridium difficile, E. coli, Campylobacter spp. and Shigella spp. and E. histolytica. Cytomegalovirus should be considered in immunocompromised individuals.

Crohn's colitis—Diagnosis is achieved by considering history, endoscopic appearance, histology and contrast radiology. When features of both UC and Crohn's colitis are present, the term 'intermediate colitis' is best used.

Other Possibilities

Ischemic colitis—Usually sudden onset, rectum not affected.
Microscopic colitis—Causes watery, not bloody diarrhoea. Diagnosis is made by finding chronic inflammatory infiltrate (lymphocytic colitis).
Radiation colitis—History of pelvic or abdominal node irradiation with mucosal telangiectasia.
Toxic megacolon is defined as a severe attack of colitis with total or segmental dilatation of colon (diameter of transverse colon usually > 5–6 cm) recognised by plain X-rays. Megacolon is considered if 2 or more of the following criteria. 1. Pulse >100/min. 2. Temp. >101.5°F. 3. Leucocytosis >10,000/mm^3. 4. Hypoalbuminemia < 3 gm/dL.
Rectal mucosal prolapse (solitary rectal ulcer syndrome) is distinguished from proctitis by characteristic histology showing muscularis interdigitation between the crypts.
Drug-induced NSAIDs may be identical to UC, but will not return once the drugs are withdrawn.

Management

Management of active UC is given in Table 34.

Refractory Disease

If initial response to corticosteroids and relapse with reduction of dose to 15 mg/day or within 6 weeks of stopping corticosteroids – Azathioprine 1.5–2.5 mg/kg/day. Monitoring full blood count every 4–6 weeks. If tolerated the drug is continued for 3–5 years to prevent relapse. Methotrexate if no response to azathioprine. Cyclosporine IV in severe UC refractory to steroids. Mycophenolate mofetil is effective in maintaining remission as also Infliximab.

Tofacitinib, an oral inhibitor of janus kinases 1, 3 is effective in moderate to severe UC in clinical trials.

Indications for Surgery

(a) Emergency surgery for severe disease, toxic dilatation of colon, perforation, severe hemorrhage. (b) Elective surgery: Acute disease that fails to respond to medical treatment, frequent relapses in spite of adequate treatment, chronic disease with permanently damaged bowels, strictures, total bowel involvement with activity extending over more than 10 years.

Colectomy with temporary ileostomy and ileoanal pouch construction is operation of choice.

Table 34: Management of active UC

Drugs	*Mild attack*	*Moderate attack*	*Severe attack*
Corticosteroids			
Prednisolone oral	20 mg/d x 1 month	40 mg/d x 1 week	Hospitalize
	15 mg/d x 1 week	30 mg/d x 1 week	Hydrocortisone 400 mg iv/day
	10 mg/d x 1 week	Then as for	Rectal hydrocortisone.
	5 mg/d x 1 week	mild attack	Fluids IV
			Potassium supplements
Corticosteroid enema	Prednisolone phosphate 20 mg in saline od or bd or Hydrocortisone 100 mg od	As for mild attacks	Metronidazole 500 mg 6 hourly iv Thromboembolism prophylaxis Toxic dilatation – Treat medically for 12–24 hrs, if no improvement (pulse, stool frequency, diameter)– Colectomy
5-ASA products	Alternative to corticosteroids	Continue unchanged	
Sulphasalazine	2 g/day		
Or Olsalazine	1.2–2.4 g/day		
or	for 6 weeks		
Mesalazine enema	1 g in 100 mL saline		

CROHN'S DISEASE

A non-specific granulomatous inflammation involving sharply demarcated single or multiple areas of the intestine, and probably a non-specific pathological response to a variety of exciting agents.

It can affect any part of the GI tract, but most commonly affects the terminal ileum or the ileocaecal region.

Aetiology

Genetic factors: About 15–20% of patients with Crohn's disease have one or more family members (usually a first degree relative) with either Crohn's disease or ulcerative colitis. Mutations in the CARD15 (NOD2) gene on chromosome 16 have been found in about one-third of patients with Crohn's disease and are particularly associated with ileal disease. Genes within the HLA region (chromosome 6p) appear to influence colonic involvement and the presence of extraintestinal manifestations.
Smoking: Smokers are more likely to develop the disease than non-smokers. Also the disease has a more unfavourable course in smokers.

Table 35: Clinical features of Crohn's disease

Disease site	*Clinical features*
Ileum	Abdominal pain
	Diarrhoea
	Obstructive symptoms
	Mass in right iliac fossa
	Acute ileitis (uncommon)
Colon	Rectal bleeding
	Perianal disease
	Extra intestinal manifestations
Rectum	Proctitis
Other sites	Mouth, stomach, duodenum affected (rarely)

Table 36: Extra-intestinal manifestations

Related to disease activity
• Aphthous ulceration
• Erythema nodosum
• Pyoderma granulosum
• Acute arthritis (large joint, transient)
• Eye complications: Conjunctivitis, episcleritis, uveitis
Unrelated to disease activity
• Sacroiliitis (usually asymptomatic)
• Ankylosing spondylitis

Infective organisms: Mycobacterium paratuberculosis has been found in tissue of a small number of patients with Crohn's disease.

Diet: High intake of refined sugar and low intake of fibre from fruits and vegetables have been reported in patients with Crohn's disease.

Immune mechanisms: There is evidence that the normal mechanisms for down-regulating mucosal immune response are impaired in patients with Crohn's disease.

Clinical Features

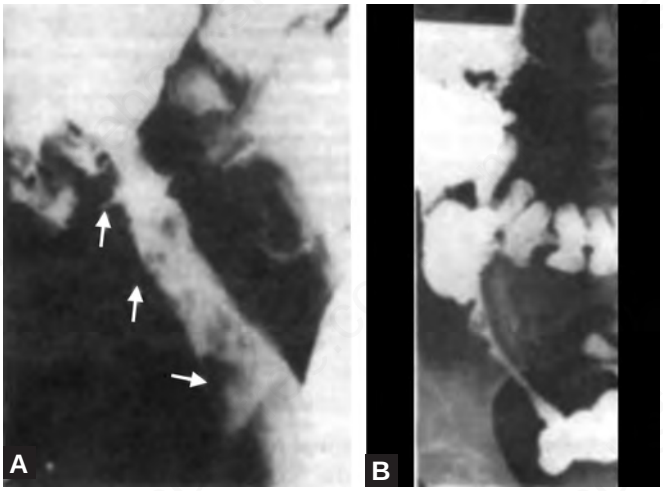
Clinical features of Crohn's disease depend on the site of disease as enumerated in Table 35. Table 36 lists the extra-intestinal manifestations of Crohn's disease.

Complications

- *Strictures*—More common in small intestine. May cause obstructive symptoms.
- *Fistulas*—may develop between loops of bowel adjacent to the bladder or vagina. Pneumaturia and recurrent urinary infections indicate fistula into the bladder. Passage of flatus or feculent vaginal discharge signifies a vaginal fistula.
- *Perianal disease*—Fissures, fistulas and abscesses. Fleshy skin tags with violaceous hue common.
- *Carcinoma of intestine*—may complicate long standing colonic disease.
- *Secondary amyloidosis* in long standing cases.

Investigations

1. ***Stool examination*** to exclude known pathogens.
2. ***Sigmoidoscopy and rectal biopsy:*** Patients with small bowel involvement may show histological evidence of rectal inflammation; this may show features of Crohn's disease (e.g. focal inflammation, granulomata).



Figs. 32A and B: (A) Small bowel enema in Crohn's disease of terminal ileum The lumen is narrowed and there is fissure ulceration (arrows); (B) Combination of transmural thickening and spasm produces the classical 'string sign' in the terminal ileum

3. ***Imaging***
   (a) Small bowel enema (enteroclysis) and an air-contrast barium enema—Crohn's disease often leads to separation of bowel loops, a normal (Fig. 32A) and ulcerated terminal ileum and in advanced cases the string sign (Fig. 32B).
   (b) Indium 111-labelled or 99 technetium-HMPAO-labelled leucocyte scans may also be helpful in demonstrating extent of inflammation if barium radiology is equivocal.
   (c) Ultrasonography may be helpful in patients with a palpable abdominal mass in order to differentiate an inflammatory mass from an abscess.
   (d) CT is often more useful and may show thickened loops of affected intestine.
   (e) MRI is the procedure of choice for investigating complex perianal disease.

Table 37: Differentiating features between ulcerative colitis and Crohn's disease

	Ulcerative colitis	*Crohn's disease*
History		
Smoking	Non-smokers	Smokers (more severe)
Family history	Occasionally	15–20%
Clinical Features		
Bloody diarrhoea	Common	Not so common
Abdominal lumps	Rare	Common
Perianal disease	Uncommon	Frequent
Signs of malabsorption	Never	Frequent
Radiology		
Rectal involvement	Invariable	Uncommon
Distribution	Continuous	Segmental
Mucosa	Fine ulceration	'Cobblestones'
	Double contour	'Rose-thorn' ulcers
Histology		
Distribution	Mucosal	Transmural
Cellular infiltrate	Neutrophils, plasma cells, eosinophils	Lymphocytes, plasma cells, macrophages
Glands	Destroyed	Preserved
	Crypt abscesses	Rare
Special features	None	Granulomas, Aphthous ulcer
		Histiocyte lined fissures
Colonoscopy/ *sigmoidoscopy*	Loss of vascular pattern, contact bleeding, ulceration and spontaneous bleeding	Deep longitudinal ulcers, skip lesions
Complications		
Rectal involvement	Invariable	Uncommon
Strictures	Rare	Common
Fistulas	Very rare	May occur

(f) Colonoscopy is useful for histological confirmation and for assessing extent of colonic involvement and for obtaining ileal biopsy specimens. Flexible sigmoidoscopy is safer because of higher risk of bowel perforation.

Table 37 enlists the differentiating features between ulcerative colitis and Crohn's disease.

Differential Diagnosis

Small intestinal disease—(a) *Tuberculosis*: Colonoscopy with multiple biopsy may be helpful and laparotomy may detect serosal tubercles. (b) *Microscopic colitis* is characterised by chronic watery diarrhoea and histopathologically by typical microscopic abnormalities in an otherwise macroscopically normal colonic mucosa. Collagenous and lymphocytic colitis are the two common forms of microscopic colitis. (c) *Other conditions* include intestinal lymphoma, carcinoid, α-chain disease, actinomycosis, amyloidosis, Behcet's disease and carcinoma.

Management

1. ***General measures***—Well-balanced diet with high fibre content. Low-fat, low-residue diet if steatorrhoea or strictures. Vitamin supplements. Rest in bed during acute phase with liquid diet. If anemia, iron by injection, or B_{12} and folic acid if megaloblastic anaemia. Codeine sulphate, diphenoxylate or loperamide helps to reduce bowel looseness.
2. ***Drug treatment***

Aminosalicylates—Sulphasalazine1 g t.d.s. orally in active colonic disease. Mesalazine delayed release 400 mg t.d.s. for maintenance therapy.

Corticosteroids—are beneficial in active disease. (a) Local therapy—Hydrocortisone suppositories for disease of rectosigmoid colon, foam or liquid enema for more proximal disease od or bd × 3–6 weeks. Prednisolone 0.25–0.75 mg/kg to maximum of 60 mg for 4 months. (b) Systemic treatment—Parenteral corticosteroids e.g. Hydrocortisone 100 mg. IV 8-hourly useful for inducing remission in severely ill patients with acute Crohn's colitis.

Metronidazole—400 mg t.d.s. if associated sepsis (e.g. in relation to fistulas or perianal disease or bacterial overgrowth of small intestine with resulting steatorrhoea).

Immunosuppressive agents—Azathioprine 2.5 mg/kg/day or 6-mercaptopurine 1.5 mg/kg/day may be used if other therapy has failed and surgical treatment is inappropriate. Regular blood count should be done to detect bone marrow suppression. Cyclosporine has rapid onset of action. IV injection at a dose of 2–4 mg/kg/day induces clinical improvement within a week. Prophylaxis against *Pneumocystis jiroveci* pneumonia is administered in all patients on the drug.

Immunotherapy—Infliximab (an IgG1 chimeric antibody to tumour necrosis factor). Single infusion of 5mg/kg i.v. Two-thirds of patients with chronic active disease resistant to corticosteroids and immunosuppression respond as also 50% with fistulas. Regular infusions every few months for maintenance. Side-effects are uncommon but include activation of latent tuberculosis, and appearance of antibodies to dsDNA with occasional manifestations of lupus-like syndrome.

Natalizumab is a recombinant humanized IgG4 anti body against α4-integrin that has been shown to be effective in induction and maintenance of patients with CD. It has been approved since February 2008 for the treatment of patients with CD refractory or intolerant to anti-TNF therapy. Side effect is progressive multifocal leukoencephalopathy (PML). The most important risk factor for development of PML is exposure to the John Cunningham (JC) polyomavirus.

Vedolizumab, leukocyte trafficking inhibitor, monocloal antibody directed against α4β7 integrin, is indicated for patients who have had an inadequate response or lost response to or were intolerant of a TNF blocker or immunomodulator or had an inadequate response or were intolerant to or demonstrated dependence on glucocorticoids. It is an option for patients who are JC antibody positive since it does not cross the blood-brain barrier.

Ustekinumab, a fully human IgG 1 monoclonal antibody, blocks the biologic activity of IL-12 and IL-23, shows efficacy in moderate to severe CD in clinical trials.

Surgical Management

Indications:

- Intestinal obstruction
- Perforation
- Failure to respond to medical therapy.
- Complications such as fistulas and perianal disease.

Limited resections, stricturoplasty or end-to-end anastomosis as necessary. Split ileostomy to isolate colon in case of fistulas and perianal disease.

23. ISCHEMIC BOWEL DISEASE

ACUTE MESENTERIC ISCHEMIA

AMI is usually caused by superior mesenteric artery (SMA) embolization or thrombosis (Fig. 33), non-occlusive mesenteric ischemia or acute mesenteric venous thrombosis. Rare causes include vasculitis, fibromuscular dysplasia, dissection, trauma and rupture of a mesenteric aneurysm.

Emboli can originate from the heart or aorta. Most emboli lodge distal to origin of middle colic artery.

Thrombosis of SMA or coeliac axis occurs as a result of underlying mesenteric atherosclerotic stenosis progressing to occlusion, usually at the origin of the vessel.

Non-occlusive mesenteric ischemia develops in patients in a low cardiac output state, particularly in presence of digoxin or vasoconstrictors. Mesenteric vasoconstriction results in segmental vasospasm of secondary and tertiary branches of the SMA.

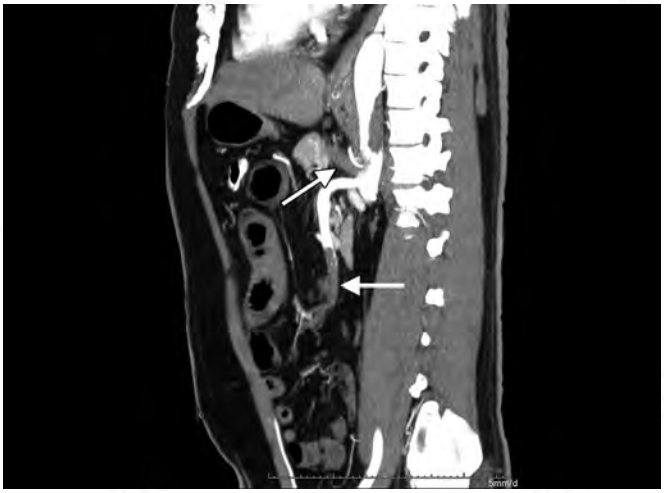


Fig. 33: Abdominal angiography showing celiac and superior messenteric artery thrombus

Mesenteric venous thrombosis may be secondary to infection, hypercoagulability states, cirrhosis, splenomegaly, malignancy, trauma or pancreatitis. Bowel oedema, impaired venous drainage and increased plasma viscosity reduce arterial inflow and may lead to bowel infarction.

Clinical Features and Diagnosis

Classically AMI presents with acute onset of abdominal pain disproportionate to the physical signs. Central abdominal pain. GI emptying may occur, with emesis and bloody diarrhoea.

Laboratory Findings

These include leucocytosis, acidosis, hyperkalemia and raised hematocrit, LDH, SGOT and creatine kinase occur later.

Imaging

CT angiography is sensitive for mesenteric occlusion. It also identifies non-vascular causes of acute abdominal pain. CT angiography with three dimensional reconstruction may show the vascular anatomy and pathology in sufficient detail for diagnosis and operative treatment.

Management

Acute SMA embolism—Balloon embolectomy, usually with patch angioplasty of the SMA. For chronic proximal occlusion or stenosis, bypass grafting. Resection of infarcted bowel after revascularization.

Acute SMA thrombosis—Replacement of a bypass graft to the SMA distal to the occlusive segment. Thrombolytic therapy is considered in acute thrombosis with no clinical signs of peritonitis.

Non-occlusive mesenteric ischemia—Any metabolic cause can be identified and corrected. The SMA is selectively catheterized and vasodilating agents such as papaverine given.

Mesenteric vein thrombosis—Fluid resuscitation and systemic anticoagulation. Thrombolysis in patients with no signs of peritonitis.

CHRONIC MESENTERIC ISCHEMIA

Clinical Features

Classical symptom is abdominal pain after eating (also termed 'mesenteric angina'). Diarrhoea secondary to malabsorption may occur. Patients become fearful of eating and thus lose weight. On physical examination an epigastric bruit may be heard. Signs of multifocal atherosclerosis are usually present.

Diagnosis

Lateral views on MDCT/MR aortography are the best means of demonstrating visceral occlusive lesions. Duplex scanning can document presence of stenosis in the visceral arteries.

Management

Mesenteric stenting—percutaneous angioplasty stent replacement in those with a suitable vascular anatomy offer long term relief from pain.

24. DRUG-INDUCED GASTROINTESTINAL DISORDERS

Drug effects on GI tract (Table 38) can be considered in four categories:

1. *Due to pharmacological mode of action*—Adverse drug reactions can occur as a predictable result of a drug's mode of action. For instance, anticholinergic agents (e.g. antidepressants) reduce oesophageal sphincter pressure resulting in reflux and heartburn, they also reduce colonic transit resulting in constipation.
2. *Impairment of GI defences*—example NSAIDs act principally by inhibiting prostaglandin synthesis.
3. *Direct injury to GI tract—example* oesophageal damage by potassium preparation, gastroduodenal ulcer by cytotoxic drugs, and ulceration and colitis associated with oral gold.
4. *Changes in colonic bacterial flora.*

Table 38: Categories of adverse effects of drugs on GI tract

	Problem	*Causative drug*
Oesophagus	Heart burn	Anticholinergic agents, tricyclic antidepressants. phenothiazines
	Oesophagitis, candida oesophagitis, strictures	Tetracycline, bisphosphonates Immunosuppressive drugs NSAIDs
		Pot chloride, quinidine (particularly slow-release preparations)
	Dyspepsia and gastroduodenal ulcers GI tract	NSAIDs, co-prescription of corticosteroids, warfarin, aspirin
Nausea and vomiting	Gut damage including ulceration	Locally irritant - Iron, NSAIDs, theophylline, and pharmacologically metronidazole
Diarrhoea	Disturb intestinal flora (e.g. C. difficile) Antagonising anti-peristaltic	Act via CNS: Levodopa, bromocriptine, opiates, digoxin, chemotherapeutic agents
	adrenergic stimulation	Cephalosporins, β-blockers
	Direct irritant action on colon	Bile acids
	Stimulation of intestinal	Misoprostol
	secretion and motility	Olsalazine
Constipation	Constipation induced abdominal pain	Antimuscarinic drugs: atropine, tricyclic antidepressants, opiates.
	Drug-induced mega colon from enteric neurotoxicity	Vincristine or possibly laxatives
	Bloating and occasionally impaction	Dietary fibres in excessive amounts
Colitis	Inflammation of the colon	Mefenamic acid, penicillamine, antibiotics, oral gold.
Malabsorption	Small intestinal disease Coeliac disease Folate deficiency	Colchicine, biguanides, laxatives, salicylates. Sulfasalazine and phenytoin cause folate malabsorption.

25. FACTITIOUS GASTROINTESTINAL SYMPTOMS AND MUNCHAUSEN

There are several syndromes that depend on lie. These may involve obvious secondary gain for example the malingerer who seeks compensation for disability. Alternatively, there may be no obvious motive, as in Munchausen's syndrome. The physician must be alert to complaints of abdominal pain, constipation, diarrhoea or vomiting when the tests are negative and the observed behaviour of the patient does not fit the complaint. The linking phenomena in such cases include elaborate, fantastic, deliberate fabrication of disease, often by someone with medical knowledge, and inexplicable, intractable and often hazardous compulsion to undergo treatment.

Munchausen syndrome is a type of factious disease characterised by simulated disease, pathological lying (often elaborate and fantastic), and wandering from place to place and hospital to hospital.

TYPES OF MUNCHAUSEN SYNDROME

- Abdominal: Patients travel to various hospitals undergoing repeated operations, only to discharge themselves against advice (even with wounds still healing and iv drips in place).
- Bleeding: Characterised by bleeding symptoms: Anticoagulant subtype, anemia subtype, pretended bleeding subtype.
- Neurological: Patients present with unusual often convincing fits, spells, faints and anesthesia
- Miscellaneous: Pyrexia, dermatological, endocrine
- Munchausen syndrome-by-proxy: A form of child abuse in which a parent or carer feigns illness in a child.

MISCELLANEOUS

Oral Manifestations of Systemic Disease

Coeliac disease occasionally produces oral ulceration, glossitis and/or angular stomatitis.

Allergic gingivostomatitis and cheilitis—Altered taste, burning or discomfort may occur as a result of food allergy to various foods, flavourings, preservatives and dental materials. In severe cases of food allergy, ulceration may occur.

Inflammatory bowel disease—Crohn's disease can manifest as tags, ulcers and/or mucosal granulomatosis leading to swelling or cobble-stoning. Ulcerative colitis may produce aphthae, chronic ulceration or pyostomatitis vegetans, which is characterized by deep fissuring and micropustules.

Behcet's syndrome is the association of orogenital ulceration with ocular disease.

Hematological disease—Hematinic deficiency may cause glossitis or ulceration. Leukemia and lymphoma may cause infections, ulcers, purpura or gingival swelling.

Genodermatoses with characteristic oral manifestations include – (a) Rendu-Osler-Weber disease with mucocutaneous telangiectasiae that are prone to spontaneous hemorrhage. (b) Cowen's syndrome characterized by circumoral and submucosal soft tissue nodules (trichilemmomas). (c) Peutz-Jeghers syndrome with mucocutaneous freckling and intestinal polyposis.

Skin manifestations of GI disease are listed in Table 39.

IMMUNODEFICIENCY AND THE GUT

Causes of Immune Deficiency

- Defects in production of secretory IgA
- Genetic defects
- Iatrogenic cellular immune deficiency (Total body irradiation or chemotherapy)
- HIV infection

Common Infections of the Intestines Associated with Immune Deficiency

- Giardia lamblia. Mainly acquired from water, but can occur in homosexual males as a result of sexual activity.
- Cryptosporidiosis is associated with chronic diarrhoea, wasting and death.
- Microsporidiosis with chronic diarrhoea and wasting

Table 39: Skin manifestations of GI disease

Condition	*GI disorder*
Erythema nodosum	Inflammatory bowel disease
Pyoderma gangrenosum	Inflammatory bowel disease
Purpura/petechiae	Bleeding disorders
Mucocutaneous pigmentation	Peutz-Jeghers syndrome
Acanthosis nigricans	GI malignancy

- Bacterial diarrhoea (Shigella, salmonella and campylobacter).
- Mycobacterium avium intracellulare. Diarrhoea is a late manifestation of HIV infection.
- Cytomegalovirus infection in patients with severe immune suppression causes bloody diarrhoea, sometimes associated with toxic dilatation and colonic perforation.

Common Infections of the Oesophagus

- Oesophageal candidiasis causes pain on swallowing.
- CMV of oesophagus produces hemorrhagic oesophagitis.
- Ulcers of unknown aetiology similar to aphthous ulcers in appearance.

Gastroparesis means incomplete or partial paralysis of the stomach. It is a disorder of delayed gastric emptying in absence of mechanical obstruction. Causes-peptic ulcer disease, endocrine disorders, (thyroid, diabetes, parathyroid, collagen vascular disease), psychogenic causes.

CHAPTER 2

Hepatobiliary and Pancreatic Disease

1. INVESTIGATING AND IMAGING THE LIVER, BILIARY TRACT AND PANCREAS

INVESTIGATIVE MODALITIES FOR LIVER STRUCTURE AND FUNCTION

- Tests indicating some form of liver dysfunction but are generally nonspecific (e.g. biochemical liver function tests).
- Tests to assess liver function and the prognosis of disease (e.g. antipyrine clearance).
- Tests to detect structural abnormalities (CT scan and USG).
- Tests to determine underlying cause of liver disease (e.g. hepatic serology).

Blood Tests

1. **Biochemical liver function tests**

   Biochemical liver function tests and their rationale and significance are given in Table 1.

Table 1: Biochemical liver function tests

Test	*Normal values*	*Significance*
Excretion		
Bilirubin		
Total	0.3–1 mg/dL	Cholestasis
Unconjugated	< 0.3 mg/dL	Hemolysis (congenital or acquired)
Urine bilirubin		Any bilirubin found in urine is conjugated bilirubin and indicates liver disease. Unconjugated bilirubin is highly bound to albumin and so not found in the urine.
Blood ammonia		Elevated in severe portal hypertension. Elevated levels correlate with outcome in severe hepatic failure.
Synthesis		
Serum albumin	3.5–5 g/dL	Low levels in a jaundiced patient suggest chronic liver disease.
Prothrombin time	12–15 sec	Prolonged in both biliary obstruction and parenchymal liver disease. > 5 seconds above control and not corrected by parenteral vitamin K administration. *Poor prognostic sign in acute viral hepatitis and other acute and chronic liver diseases.*
Tests reflecting cholestasis		
Serum alkaline phosphatase (AP)	30–120 IU/L	Intrahepatic or extrahepatic cholestasis. Early marker of liver metastases or abscess formation.
Serum gamma-glutamyl transpeptidase (GGT)	10–50 IU/L	May occur with focal hepatic lesions in absence of jaundice. In cholestasis, alkaline phosphatase (AP) is higher than GT, reverse in alcoholic liver disease and patients taking enzyme reducing agents. Used to identify patients with occult alcohol use.
Tests reflecting liver cell injury		
Serum aspartate aminotransferase (AST) Serum alanine aminotransferase (ALT)	5–40 IU/L 5–35 IU/L	Transaminases elevated in presence of liver cell injury. >1000 IU/L seen in (1) viral hepatitis, (2) ischemic liver injury, (3) toxin and drug induced injury.
AST:ALT ratio		<1 in chronic viral hepatitis and non-alcoholic steatohepatitis. >1 as cirrhosis develops

Table 2: Tumour markers in carcinoma of liver

Tumour marker	*Significance*
α-fetoprotein (AFP)	Hundred fold elevated in 80% in primary liver cell cancer and germ cell tumours. Elevated in oanly 50% heapatocellular carcinoma of patients. Modest elevation (up to 10 times normal), may be seen in active inflammation or regeneration, but progressively rising AFP of ominous significance. Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) assay is thought to be more specific.
des-y-carboxy prothrombin (DCP)	A protein induced by vitamin K absence (P1VKA-2). Increased in as many as 80% of HCC patients. May also be elevated in patients with vitamin K deficiency. It is always elevated after warfarin use. It may also predict for portal vein invasion.
Carcinoembryonic antigen (CEA)	In follow-up of patients with treated colon cancer, in whom rising CEA levels may indicate presence of metastases in the liver.

Both AFP-L3 and DCP is US Food and Drug Administration (FDA) approved as serological assay in hepatocellular carcinoma.

2. **Hepatitis serology** is described in diagnosis of types of hepatitis virus infections.
3. **Tumour markers**

   Tumour markers elevated in carcinoma of liver are given in Table 2.
4. **Autoantibody and immunoglobulins characteristics of liver disease**

   Autoantibody and immunoglobulins characteristics of liver disease are listed in Table 3.
5. **Alcoholic aetiology** in a patient with liver disease is suggested by:

   Parotid enlargement

   Dupuytren's contracture

   Increase in:

   Gamma-glutamyl transpeptidase

   Raised MCV

   Decreased transferrin

   Serum IgA

   Aspartate aminotransferase alanine aminotransferase ratio

   >2:1 Suggestive of alcoholic liver disease

   >3:1 Highly Suggestive of alcoholic liver disease

Table 3: Autoantibody and immunoglobulins characteristics of liver disease

	Autoantibodies	*Immunoglobulins*
Primary biliary cirrhosis	High titre of antimitochondrial antibody in 95%	Raised IgM
Autoimmune chronic active hepatitis	Smooth muscle antibody in 70%, antinuclear factors in 60%	Raised IgG in all patients
Primary sclerosing cholangitis	Low antibody antimitochondrial antibody titre in 20%. Antinuclear cytoplasmic antibody *(p-ANCA)* in 30%.	

6. **Other blood tests**

   Other blood tests useful in evaluation of liver disease are listed in Table 4.

Imaging Techniques

Plain abdominal radiography

- Gallstones
- Air in biliary tract
- Pancreatic calculi
- Calcified gallbladder (rarely)

Ultrasonography

- Presence of ascites
- Investigation of jaundice
- Hepatomegaly/Splenomegaly
- Detection of gallstones
- Focal liver disease (lesions > 1 cm)
- General parenchymal liver disease
- Excellent view of pancreas
- Assessment of patency of portal and hepatic veins
- Abdominal lymph node enlargement
- Intraoperative ultrasonography

Doppler USG

- For thrombosis of hepatic and portal veins

Transient elastography and Magnetic resonance elastography.

Transient elastography (TE), marketed as FibroScan,

TE uses ultrasound waves to measure hepatic stiffness noninvasively.

Accurate for identifying advanced fibrosis in patients with

Table 4: Other blood tests in evaluation of liver disease

Test	*Significance*	
Haematological		
Full blood count	Bleeding produces microcytic hypochromic anaemia	
	Alcohol causes macrocytosis, sometimes leucopenia, thrombocytopenia	
	Haemolysis occurs with acute liver failure	
Biochemical		
a-antitrypsin	Deficiency can cause cirrhosis	
Serum copper	Raised in Wilson's disease	
Ceruloplasmin	Decreased in Wilson's disease. May occasionally be normal in Wilson's causing chronic hepatitis. Raised in hepatic encephalopathy but no correlation with severity	
Serum iron and	Raised in hemochromatosis	
Serum ferritin		
Serum ammonia	Raised with serum globulin in most cases of chronic hepatitis	
Serum creatinine	Raised in hepatic failure and indicates impending onset of hepatorenal syndrome	
Amylase	Pancreatitis	Ca lung
	Ca pancreas	After ERCP
	Acute cholecystitis	Burns
	Mesenteric thrombosis and infarction	Ruptured tubal pregnancy
	Parotitis	Macroamylasemia
	Mumps	Acute ethanol ingestion
	Renal disease (end stage)	Diabetic ketoacidosis Post-op. abdominal surgery
Lipase	Same as amylase (except not in parotitis, mumps, macroamylasemia)	

1. chronic hepatitis C
2. primary biliary cirrhosis
3. haemochromatosis
4. non-alcoholic fatty liver disease and
5. recurrent chronic hepatitis after liver transplantation.

MRE

It has been found to be superior to TE for staging liver fibrosis but requires access to a magnetic resonance imaging scanner.

Transient elastography (TE) and magnetic resonance elastography (MRE) both have gained U.S. Food and Drug Administration approval for use in the management of patients with liver disease.

Oral cholecystography is best reserved for patients in whom ultrasonography is equivocal or is negative despite a strong clinical suspicion of gallbladder disease. It can be diagnostic of adenomyomatosis$_2$.

CT

Spiral CT

Scans can be obtained quickly and hence images at different phases of liver enhancement after bolus contrast injection is possible; e.g. one scan at 40 seconds after injection demonstrates the hepatic arterial phase optimally, and a second scan at 80 seconds shows the portal phase. This biphasic technique can detect and characterise liver abnormalities. With multi-slice CT much faster scans are possible.

CT arterioportography (following placement of an arterial catheter in coeliac axis or superior mesenteric artery), a high contrast dose delivered to the liver leads to detection of more metastases because these enhance differentially compared to the background liver.

CT cholangiography (following infusion of iv cholangiographic contrast) can show the biliary tree in detail provided liver function is normal.

MRI—(a) Unenhanced MRI is comparable to enhanced spiral CT and better than ultrasonography in detection of liver lesions. (b) The technique can provide excellent non-invasive reconstructions of the bile ducts. (c) Contrast-enhanced MRI—'Life specific' agents e.g. iron oxide particles taken up by Kupffer cells, chelates of manganese taken up by hepatocytes. (d) MRI is a good 'one-stop' investigation for the liver, providing excellent anatomical detail and good lesion detection and characterization, and enabling assessment of the biliary tree, portal and hepatic arterial systems and related organs such as the pancreas and spleen. (e) Liver fat quantification—By comparing the signal intensity of hepatic fat by out-of phase (OP) and in-phase (IP) imaging. Signal loss of OP images indicates presence of fat, lack of signal loss suggests absence of fat.

Isotope scanning of the hepatobiliary system. Use of radionuclide in liver imaging has declined with availability of other imaging techniques. Uses include—

- Tc labelled RBCs to assess liver haemangioma.
- A combination of Tc-colloid and gadolinium-67 is used to differentiate hepatocellular carcinoma (increased vascular flow) from regenerative nodules of cirrhosis (diminished flow).
- 99mTc-iminodiacetic acid derivatives used to evaluate cystic duct patency. These agents have the advantage that they can be used at higher levels of bilirubin than iodinated cholecystographic media.

- Positron emission tomography (PET) by using labelled somatostatin analogues has the advantage of highlighting both primary and secondary tumors in a single scan.

Magnetic Resonance Cholangiopancreatography (MRCP)

This technique involves manipulation of data by MRI. A heavily T_2 weighted sequence enhances visualization of the 'water-filled' bile ducts and pancreatic duct to produce high quality images of ductal anatomy and allows noninvasive visualization of bile and pancreatic ducts. It is superseding most diagnostic endoscopic cholangiopancreatography.

Angiography

Selective catheterization of coeliac axis and hepatic artery for detection of abnormal vasculature in hepatic tumors. Angiography does not detect GI bleeding at rates below 0.1 mL/min, but readily reveals underlying vascular abnormalities. In digital vascular imaging (DVI) contrast given IV or intra-arterially can be detected in the portal system using computerised subtraction analysis. Visualization of hepatic veins by venography is useful in diagnosis of Budd-Chiari syndrome.

Endoscopy

Endoscopic Ultrasonography

- Excellent views of pancreas, portal veins and biliary tree may be obtained.
- Intraoperative ultrasonography performed by direct application of a sterile probe onto the liver surface.
- Ultrasound contrast media are used to assess some liver tumors.

Endoscopic retrogradecholangiography (ERCP) is a procedure that combines the use of X-rays and/or endoscopy.

Indications

Biliary tree

- Obstructive jaundice (Stones, sclerosing cholangitis, focal liver parenchymal lesions).
- Postcholecystectomy syndrome
- To delineate intrahepatic biliary radicles
- Primary biliary cirrhosis

Pancreas

- Pancreatic carcinoma
- Chronic pancreatitis (Pre-operative)

Table 5: Indications for liver biopsy

Indications	*Examples*
Assessment of chronic liver disease	Severity of liver disease (e.g. whether cirrhosis is present) and assessing degree of disease activity (e.g. in chronic hepatitis) Determining cause of liver disease (e.g. stains for iron, hepatitis B and α-antitrypsin may establish aetiology of cirrhosis)
Investigation of acute hepatic dysfunction	Useful if diagnosis is in doubt (e.g. suspected drug reaction), or if course of severity of illness is unusual
Targeted biopsy for focal lesions	Focal lesions such as primary or secondary liver tumors
Investigation of systemic disease and PUO	To establish diagnosis in difficult cases (e.g. sarcoidosis, tuberculosis, amyloidosis, glycogen storage disease, lymphoma)
Assessment of liver transplantation	Liver histology is essential in potential transplant recipients. Serial biopsy of the grafted liver is an important means of detecting early rejection and other complications.

- Pancreatic lithiasis
- Pancreatic pseudocyst
- Pancreatic duct leaks

Percutaneous transhepatic cholangiography (PTC) is used to visualise intrahepatic and extrahepatic biliary tree.

Liver Biopsy

Indications for liver biopsy are listed in Table 5.

Contraindications

- Coagulopathy
- Patient inability to cooperate with the breathing manoeuvres needed for percutaneous biopsy (e.g. mental retardation, impaired consciousness, respiratory disease).
- Large ascites
- Suspected extrahepatic obstruction

Standard Percutaneous Biopsy

Preparation—Prothrombin time should not be > 3 seconds. Platelet count at least 80×10^9/L.

Administration of vitamin K and fresh frozen plasma if clotting parameters are borderline. Blood for grouping and cross-matching.

Biopsy site—Mid-axillary line just below upper limit of hepatic dullness. Local anaesthesia (2% lignocaine) is given from the skin down to the liver capsule. The biopsy is taken, with patient's breathing suspended in expiration,

Table 6: Complications of liver biopsy

Complication	*Comment*
Puncture of gallbladder or major bile ducts	Bile leakage causes immediate severe abdominal pain progressing to biliary peritonitis.
Haemobilia (bleeding into biliary tree)	May present with GI haemorrhage, colic and jaundice.
Cholangitis	May occur particularly with bile duct obstruction.
Puncture of viscera	Puncture of kidney or colon usually without sequelae. Pancreatic puncture may be serious.
Intrahepatic haemangiomas or arteriovenous fistulas	Heal spontaneously.

from the periphery of the right lobe of the liver. If a sample cannot be obtained or is inadequate after two attempts, the procedure should be repeated at a later date under ultrasound guidance.

Biopsy needles—These are of the aspiration type (Menghini) or cutting type (Tru-cut). The aspiration type is easier to perform, but has the disadvantage of potential sample fragmentation, particularly in cirrhosis. The external diameter of the needles is 1.6–2 mm.

Imaging—Taking a biopsy under imaging control is particularly helpful in locating a focal target lesion, but is also useful when the liver is small and difficult to localize by percussion.

Complications

Complications of liver biopsy are given in Table 6.

Alternative procedures—These are indicated if coagulopathy cannot readily be corrected and the risk of bleeding is greater.

Plugged biopsy—It is similar to standard biopsy, but an absorbable gelatine sponge is injected into the tract in the liver after the biopsy is withdrawn. The technique requires the patient to hold the breath a few seconds longer.

Transjugular liver biopsy—It is preferred in patients with significant coagulopathy because the sample is taken from within the liver via a catheter in the hepatic vein. A special tru-cut needle is inserted through a catheter placed in the hepatic vein via the jugular vein and a sample taken from within the liver. The advantages are the facility for multiple biopsies and simultaneous pressure measurements and venography. Also in patients with small livers.

Laparoscopic biopsy—is of particular value for target biopsy of focal lesion such as primary or secondary liver tumors.

2. VIRAL HEPATITIS

The term viral hepatitis refers to infections of the liver caused by five well-characterised hepatotrophic viruses, which are designated hepatitis A, B, C, D and E. Infections with other viruses such as Epstein-Barr (EB) virus, cytomegalo virus (CMV) and herpes simplex virus (HSV), but the liver is not the primary site for replication and cellular damage.

Acute viral hepatitis may be asymptomatic, marked only by an increase in aminotransferase levels, or symptomatic with or without jaundice or subfulminant or fulminant depending on the causative agent. Though the natural history of acute hepatitis can vary according to the etiological agent, it can be divided as follows depending on clinical features and laboratory findings:

1. *Prodromal period*
   - Bilirubinuria appears earlier than a rise in serum bilirubin.
   - Serological viral markers help in arriving at a diagnosis.
   - Urobilinogen and total bilirubin rise occurs before clinical jaundice.
   - Liver enzymes AST and ALT are > 500 units
   - Leucopaenia may be observed with onset of fever.
2. *Acute icteric stage*
   - Bilirubin rises, plateaus and then gradually decreases.
   - Serum AST and ALT rise and fall rapidly and reach normal range in 2 to 5 weeks.
   - ESR is raised initially and falls during convalescence.
3. *Defervescent stage*
   - Diuresis occurs at onset of convalescence.
   - Bilirubinuria disappears, serum bilirubin is still increased.
   - Urine urobilinogen increases.
   - S. bilirubin becomes normal after 3 to 6 weeks.

HEPATITIS A

Transmission

The main route of transmission is faeco-oral, occasionally, HAV is transmitted by blood products or through illicit use of injectable drugs.

Pathogenesis

HAV replication occurs predominantly in hepatocytes without cytopathic effect; large quantities of virus are secreted into biliary canaliculi. In addition to faecal shedding of the virus, there is sustained viraemia which persists from the earlier phase of HAV infection until onset of liver injury.

Liver injury is immune mediated by natural killer cells, virus-specific CD8+ cytotoxic T lymphocytes and nonspecific cells recruited at the site of inflammation.

Clinical Features

Incubation period 2–6 weeks, related to the infecting dose. Prodromal symptoms consist of malaise, loss of appetite, nausea, vomiting and fever. Onset of dark urine is usually the first indication of disease, followed by jaundice and pale stools. Colour returns to the urine and stools after 2–3 weeks.

In most patients HAV infection is benign. Age is the most important determinant of the severity of hepatitis A as also presence of chronic liver disease.

Complications

Include: (a) Cholestatic hepatitis with itching and jaundice lasting up to 18 weeks. In such cases a short course of rapidly tapered corticosteroids may accelerate resolution. (b) Relapsing course with a second hepatitis flare 30–90 days later; this resolves without chronic sequelae.

Viral Hepatitis in Pregnancy

Viral hepatitis in pregnancy is an important cause of foetal wastage. Hepatitis E is one of the commonest causative organism of hepatitis during pregnancy. The presence of systemic inflammatory response syndrome (SIRS) is a significant factor increasing the rates of hepatitis as cause of maternal mortality. The increasing bilirubin, features of encephalopathy and appearance of coagulopathy are all important factors for increasing maternal mortality.

Diagnosis

Nonspecific Lab Tests

- Raised serum bilirubin (5 to 10 times normal) within few days and remains high up to 12 weeks.
- Serum AST and ALT levels remain high for 1 to 3 weeks
- Alkaline phosphatase level is only mildly elevated, though if it remains persistently high, it suggests hepatitis-associated cholestasis.

Specific Tests

- Hepatitis A specific IgM antibody can be detected at the onset of symptoms and at the first rise in serum ALT. It peaks within the first month and remains positive for 3–6 months.
- IgG anti HAV becomes positive at onset of illness and is detectable for many years. It is found in about 25% of adult population indicating previous exposure to the virus.
- Nucleic acid based tests like PCR performed on stool have little role to play in clinical settings.

Managementis Supportive

Bed rest, fluid intake in form of fruit juices, sugar cane juice, avoidance of physical exertion and of alcohol. Patients at risk of complications should be monitored frequently.

Prophylaxis

Hepatitis A Vaccine

Dose primary course of 2 doses (1 mL each) one month apart. Booster Dose—One dose of 6–12 months after first dose for active immunization which provides long-lasting immunity. Apart from individuals at high risk, hepatitis A vaccination is recommended in patients with chronic hepatitis C.

Post-exposure Prophylaxis

For intimate contacts (household, sexual, institutional) of persons with hepatitis A.

Dose: Immunoglobulin 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure.

HEPATITIS B

HBV infection is parenterally transmitted:

- In babies born to HBV infected mothers, after transfusion of blood and blood products.
- IV drug use
- Sexual contact
- HDV infection only in HBV-infected individuals.

Clinical Presentation of Hepatitis B

On exposure to Hepatitis B virus, the spectrum of clinical presentation depends on the immune status of the individual.

1. ***Acute hepatitis B***—Appropriate immune response in majority of adults leads to acute hepatitis within 5 weeks to 5 months of exposure to infection but resolves within 6 months after the onset. No treatment is required as the body is able to clear the virus with the resolution of hepatitis, and clearance of virus markers and development of immunity.
2. ***Acute and subacute liver failure*** is a severe form of acute hepatitis that is complicated by liver failure. Paradoxically hepatitis B virus may be present in extremely

Table 7: Interpretations of various markers of Hepatitis B infection

Markers	*Interpretation*
HBsAg	Indicates presence of virus in the body
HBeAg	Active replication of the virus
HBe antibody	Indicates seroconversion and non replicative state
IgM anti-HBc	Indicates recent infection or acute flare of chronic infection. Low levels in chronic infection
IgG anti-HBc	Indicates remote past infection
HBs antibody	Indicates immunity against the infection either natural or following vaccine
HBV-DNA quantitative	Indicates viral load

Table 8: Hepatitis B serology and transaminases in clinical situation

Clinical situation	*Viral markers*	*ALT/SGPT*	*Comment*
Acute hepatitis B	HBsAg positive IgM anti-HBc +ve	>10 x ULN	No treatment required, spontaneous recovery
HBeAg +ve	HBsAg +ve/HBeAg +ve HBV-DNA >20,000 IU	↑	Treatment may be required
HBeAg –ve	HBsAg +ve/HBeAg –ve	↑	Treatment may be required
Chronic hepatitis B	HBV-DNA >20,000 IU		
Inactive	HBsAg +ve/HBeAg –ve	N	Treatment may not be required
Carrier	HBV-DNA low (<2000 IU)		
Resolved hepatitis B	HBsAg –ve	N	No treatment
Successful vaccination	HBs antibody +ve	–	Protection against infection

low quantity or be undetectable due to profound and inappropriate immune response. Antiviral therapy is indicated but liver transplant may be required if the condition does not stabilise.

3. ***Chronic hepatitis B***—Persistence of Hepatitis B infection for more than 6 months is seen when the body has either inadequate or no response to HBV and is unable to clear the virus resulting in chronic inflammation of the liver of variable intensity. The entire clinical spectrum of HBV infection can be classified and interpreted on appropriate selection of tests:

Serology in Hepatitis B

Interpretation of various serological markers in hepatitis B is given in Table 7. Table 8 summarises clinical situations in hepatitis B infection and serological markers and transaminase levels.

Management of Chronic HBV Infection

Management of chronic HBV infection is as follows:

1. *Replication of the virus* must be checked. HBeAg positive and anti-HBe negative indicate a replicating virus.
2. *Evidence of accompanying liver disease:*
   (a) Serum ALT/AST are the indicators for ongoing inflammation. Treatment is necessary, and effective where ALT and AST are elevated 2 × upper limit of normal.
   (b) Assess extent of liver damage which already exists by clinical evidence of splenomegaly and ascites and biochemical evidence of low platelet count, prolonged prothrombin time, low albumin, high globulin and USG findings of nodular liver and collaterals.
3. *Treatment of* the patient should then be decided according to replicative status of the virus and accompanying liver injury. The goal of treatment would be to ensure loss of HBV DNA. This is usually indicated by normalization of ALT at end of therapy with conversion of HBeAg positivity to anti HBeAg positivity in antigen positive chronic hepatitis B.

Table 9 lists antiviral drugs used in chronic hepatitis B infection and Table 10 gives the factors that determine the choice drugs for treatment.

Table 11 depicts the treatment guidelines for chronic hepatitis B virus infection as per American Association for the Study of Liver Diseases (AASLD).

Table 9: Antiviral drug in chronic hepatitis B

Drugs	*Pros*	*Cons*
Entecavir	Most potent	High cost
	High genetic barrier for resistance < 1% Resistance at 6 years	Not recommended in pregnancy 22% resistance in Lam-R at 2 years
Tenofovir	Potent data in HIV/ HBV co-infection	Renal toxicity
	No resistance at 96 weeks	Long term data needed
Adefovir	Low cost effective in Lam-R	Inefficient hence 30% resistance at 4 years
		Renal toxicity in decompensated
Telbivudine	Potent Safe in Pregnancy	22% resistance at 2 years, 4% at 48 weeks even if HBV-DNA undetectable at 24 weeks
Lamivudine	Potent, low cost, safe in last trimester of pregnancy	Low genetic barrier for resistance 70% resistance of 5 years.
Combination Lam and Adefovir	Low cost/proven benefit in makes logical sense	Unproven role in native?

Table 11: AASLD guidelines for the treatment of chronic hepatitis B virus infection

HBeAg Positive	
Indication for treatment	HBV-DNA >20000 IU/mL and ALT >2 times upper normal limit
When to biopsy	HBV-DNA > 20000 IU/mL and ALT >1- 2 times upper normal limit especially if age >40 year or family history of HCC
Recommended drugs	PEG IFN, Entecavir, Tenofovir
HBeAg Negative	
Indication for treatment	HBV-DNA >20000 IU/mL and ALT >2 times upper normal limit
When to biopsy	HBV-DNA >2000 IU/mL and ALT >2 times upper normal limit
Recommended drugs	PEG IFN, Entecavir, Tenofovir
Cirrhosis	
Indication for treatment	Compensated: HBV-DNA >20000 IU/mL or HBV-DNA > 2000 IU/mL and ALT >2 times upper normal limit. Decompensated: any detectable HBV-DNA
Recommended drugs	Oral agents in case of decompensated patients

Table 10: Factors influencing choice of therapy

Interferon	*Oral antiviral*
• Peginterferon an option in a patient with	• Choice of oral agent dependent on
– Genotype A	– Potency: Highest with entecavir and tenofovir
– Low HBV-DNA	– Rate of resistance: lowest with entecavir and tenofovir
– High ALT	– Cost: lowest with lamivudine and adefovir; generic tenofovir
– No comorbidities	– Safety: good for all oral agents
– Desire for a fixed duration of therapy and avoidance of resistance	– Special circumstances, eg, pregnancy (telbivudine class B and lamivudine good safety experience)
	– HIV coinfection

Table 12: Recombinant hepatitis B vaccine

Age	*Recombivax-HB dose*	*Engerix-B dose*
<20 years	**5 µg (0.5 mL)**	**10 µg (0.5 mL)**
>20 years	**10 µg (1 mL)**	**20 µg (1 mL)**
Haemodialysis patients		
<20 years	**5 µg (0.5 mL)**	**10 µg (0.5 mL)**
>20 years	**40 µg (4 mL)**	**40 µg (2 mL)**

Pre-exposure Prophylaxis

It is indicated in:

1. Health workers
2. Haemodialysis patients and staff
3. Injection drug abusers
4. Haemophiliacs and Thalassemia patients who need frequent transfusions
5. Homosexuals
6. In patients with sexually transmitted disease
7. High risk behaviour, multiple sexual partners, commercial sexual worker

Hepatitis B immunization have been included in national immunization programme.

Dose: Recombinant vaccine is available depending on type dose as given in Table 12.

Schedule followed is at 0, 1 and 6 months usually 3 dosages but in case of Engerix-B dose schedule is 0, 1, 2 and 6 months for haemodialysis patients.

For haemodialysis patients, annual anti-HBs testing are recommended after vaccination; booster doses are recommended when anti-HBs levels fall to < 10 mIU/mL.

Post-exposure Prophylaxis for HBV

- Wash exposed area with soap and water
- Do anti HBs levels if prior vaccination
- Take HBIG 0.06 mL/kg (if not vaccinated)
- Take vaccine 1 mL + HBIG if Anti HBs levels < 10/or unvaccinated

HEPATITIS C

HCV is a small, enveloped RNA virus and a member of the Flaviviridae.

Individuals at Risk of HCV Infection

- Injecting drug users
- Health-care workers
- Individuals on haemodialysis
- High-risk sexual practices
- Unsafe injections or other parenteral exposure to blood
- Use of blood-contaminated implements for circumcision or surgery
- Acupuncture
- Tattooing, ear piercing/body piercing
- Mother-infant transmission can occur in mothers with high levels of viraemia (particularly HIV-HCV-co-infected mothers).

Acute Hepatitis C

Incubation period 6–12 weeks. Infection is clinically mild. Only 25% are icteric, but patients with jaundice are more likely to clear the virus.

Chronic Hepatitis C

Most cases are not preceded by clinically apparent icteric hepatitis. Serum aminotransferase levels remain abnormal after 12 months in 60–85% of patients with type C post-transfusion or sporadic hepatitis.

Cirrhosis develops within 10 years in about 10–20%, but remains indolent and is only slowly progressive after a prolonged period of time. Greater age at infection, concomitant alcohol intake, concurrent HBV or HIV infection or other illness may be important aggravating co-factors. Anti-HCV persists for years or even decades in chronic HCV infection. HCV RNA usually persists in patients with abnormal serum aminotransferases and anti-HCV. Polymerase chain reaction (PCR) analysis is sensitive and specific for HCV RNA in blood and other tissues.

The infection causes systemic disease and may be associated with various complications, including a form of autoimmune cryoglobulinemia, porphyria cutanea tarda, lymphocytic sialadenitis and membranous glomerulonephritis. HCV infection is associated with non-Hodgkin lymphoma.

Diagnosis

Specific Markers for HCV Infection

1. *Antibodies to HCV* (anti-HCV)
   - Detection of antibodies to recombinant HCV polypeptides. Enzyme immunoassays (EIA) measures antibodies against two antigens NS4 and NS3
   - These assays can detect antibodies within 6 to 8 weeks of exposure
   - Average time for seroconversion is 2 to 3 weeks
2. Recombinant immunoassay (RIBA)
3. Hepatitis C virus RNA testing qualitative test
4. Hepatitis C virus RNA testing quantitative test
5. HCV genotyping is helpful in predicting response to therapy.

Treatment

Assessment for Treatment

(a) *Evaluation of virological status in anti HCV positive individual*—Immune assays (EIA) to HCV are highly sensitive in immunocompetent patients. Genotyping may be done before starting treatment for further quantifying the amount of virus and the Genotype.

Patients who are immunocompromised or on dialysis may have false negative anti HCV test due to poor antibody response. HCV RNA is necessary to confirm presence of the virus. After exposure HCV-RNA becomes detectable in serum after 7 to 9 days. Followed by aminotransferase elevation and later (after 4–10 weeks) by presence of antibodies.

In event of Anti HCV test in a blood donor, confirmation of presence of virus is required by highly sensitive ELISA test.

(b) *Assessment of liver dysfunction*—AST/ALT values if abnormal would suggest necroinflammation. Liver biopsy helps in assessment of severity of liver disease as the grade of inflammation and stage of fibrosis are not indicated by value of AST/ALT.

Table 13: Indications for treatment of hepatitis C

Should be treated	*Treatment may be individualized*	Treatment contraindicated
Chronic hepatitis C **With** Abnormal ALT **With** Liver biopsy showing significant inflammation and fibrosis **With** compensated liver disease	1. Acute hepatitis C not resolving within 3 months 2. Chronic Hepatitis C with normal ALT and AST but with significant inflammation and fibrosis on liver biopsy 3. Active substance abuse	Decompensated liver disease Post kidney transplant Associated: 1. Severe comorbid illness 2. Unconscious psychiatric illness 3. Autoimmune conditions 4. Pregnancy

(c) *Specific issues in pretreatment evaluation*
- Haematology: Estimation of WBC and platelet count and Hb.
- Estimation of thyroid function and ANA
- Psychiatric evaluation
- Testing for HBsAg and HIV coinfection
- Pregnancy – Interferon is contraindicated

Table 13 gives the indications for treatment of hepatitis C.

Combination therapy with conventional/pegylated interferon and Ribavirin is the standard treatment for chronic hepatitis C.

Other options are directly acting antiviral (DAA) agents, interferon-free combinations, which are found to have high cure rate and better compliance. These are Sofosbuvir, Ledipasvir, Simeprevir, Paritaprevir, Ombitasvir and Dasabuvir. But their high cost is main limitation for widespread use and availability in India.

Table 14 gives Indian National Association for Study of Liver.

Interferon

Dose of 3 million unit sc 3 times a week. Pegylated interferon dosage is weight based in Peg IFN2B (1–1.5 μg/kg) and standard dose of 180 mg in PegIFN2A.

Ribavirin

Treatment varies according to the Genotype. In Genotype I, Pegylated IFN is preferred and duration of therapy needs to be extended to 48 weeks with dose at 1000 mg/day if body weight < 75 kg and 1200 mg/day if >75 kg in Genotype II and III, response rates are much better and with Ribavirin at 800 mg/day with Pegylated IFN and duration of treatment 24 weeks.

Table 14: INASL 2014 guidelines for hepatitis C management

For HCV Genotype 1, 4, 5, 6	
Interferon-eligible	Peg-IFN (2a or 2b) + weight-based Ribavirin 15 mg/kg for 48 weeks
Interferon-ineligible	Directly acting antivirals (DAA)
For HCV Genotype 2, 3	
First-line therapy	Directly acting antivirals (DAA) or Peg-IFN (2a or 2b) + weight-based Ribavirin 15 mg/kg for 24 weeks
Alternative regimen	Peg-IFN (2a or 2b) + weight-based Ribavirin 15 mg/kg for 24 weeks

Special Situations in Management of HCV Infection

1. Acute HCV infection is most often symptomatic. Treatment is indicated in persons exposed to Hepatitis C and those who have HCV-RNA positive 3 months after acute infection.
2. Patients with CKD may get exposed to Hepatitis C during haemodialysis and develop hepatitis. They do not tolerate treatment well and have high chances of Ribavirin-induced haemolysis and anaemia. PEG IFN can be given in reduced doses. It is important to treat before a renal transplant to avoid possibility of rejection.
3. Patients with chronic Hepatitis C and normal SGOT, SGPT may be considered if liver biopsy shows significant fibrosis.
4. Treatment in HIV co-infection—Peg IFN and Ribavirin combination is preferred therapy. Use of erythropoietin and Granulocyte stimulating factors is advisable to avoid side effects.
5. Treatment of non-responders and relapses—Retreatment with longer duration and optimized dose of Ribavirin or changing the type of interferon may help.
6. Liver transplantation—Hepatitis C is one of the most common indication in decompensated liver disease. Monitoring postoperatively with serial liver biopsies is necessary and appropriate therapy can be given if HCV recurrence is associated with significant disease on histology of the new liver.

Post-exposure Prophylaxis

- No vaccine for C virus

  Check Anti HCV/SGPT for prior exposure
- HCV-RNA and not Anti-HCV test of choice within 12 weeks of exposure

Table 15: Viral hepatitis and their salient features

Disease	*Incubation Period*	*Mode of Transmission*	*Family*	*Nucleic Acid*	*Salient Features*	*Mortality*
Hepatitis A	2 to 6 weeks	Enteric	Picornaviridae	RNA	Acute and self-limiting, never causes liver disease	1% to 2%
Hepatitis B	4 to 24 weeks	Parenteral	Hepadenaviridae	DNA	Acute liver disease with chronic disease and risk of hepatic carcinoma	15–25% in chronically infected patient
Hepatitis C	2 to 26 weeks	Parenteral	Hepacivirus	RNA	Chronic liver disease (85%) with the risk of hepatic carcinoma (20%)	
Hepatitis D	3 to 7 weeks	Parenteral	Viroid deltaviridae	RNA	Depends on HBV for replication and expression	
Hepatitis E	4 to 6 weeks	Enteric	Hepeviridae	RNA	Water borne epidemics. Acute self-limiting hepatitis. No carrier state or chronic disease	90% mortality in fulminant cases, more often seen in pregnancy

- Spontaneous clearance likely if post exposure icteric illness
- Treatment for HCV required if HCV-RNA positive 1–3 months after exposure.

HEPATITIS D VIRUS INFECTION

- HDV virus infection should be considered in any individual who is HBsAg positive (super infection) or has evidence of recent HBV infection (coinfection). HDV is an RNA-deficient virus and hence requires presence of HBV infection.
- During HDV infection both IgM and IgG antibodies can be detected in serum in acute phase.
- HDV infection can also be detected using Reverse Transcription Polymerase chain reaction.
- Chronic HDV infection is more severe with higher mortality than other types of viral hepatitis. Cirrhosis occurs in 60 to 80% of patients with increased risk of hepatocellular carcinoma.

HEPATITIS E VIRUS

- The infection is often self-limited but may cause hepatitis of varying degree of severity. Fulminant HEV infection is often reported in pregnant women.
- Laboratory diagnosis: Identification of IgM antibodies to HEV from acute plasma serum samples (ELISA and Western block technologies). Antibodies detected are against the ORF (Open Reading Frames) 2 and ORF 3.
- Peak titres for IGM are observed during first 4 weeks while onset of infection. A rising titre of IgG antibodies is also diagnostic of infection.
- Molecular assays are used only for epidemiological studies.

Table 15 gives a brief overview of the different viruses implicated in the causation of hepatitis and their salient features.

Drug-induced hepatitis: (a) Direct toxic type related toxicity, short latent period, no extrahepatic manifestations. (b) Idiosyncratic type—most often dose related, variable latent period and presence of extrahepatic manifestations such as fever, rashes, arthralgia and eosinophilia.

Dengue fever hepatitis.

3. AUTOIMMUNE LIVER DISEASE

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is an unresolving inflammation of the liver of unknown cause that is characterized by:

- Hypergammaglobulinemia
- Auto-antibodies in the serum
- A history of other autoimmune disorders.

Clinical Features

Classic type 1 autoimmune hepatitis—May present insidiously with anorexia, nausea, malaise and fatigue. Most patients have palmar erythema and spider naevi. Some patients develop moon facies, buffalo hump, truncal obesity and abdominal striae (before corticosteroid treatment). Mild to moderate elevations of serum transaminases are common.

In some patients onset is relatively rapid resembling acute viral hepatitis with jaundice, multiple spider naevi, tender hepatomegaly and ascites. Laboratory findings indicate severe liver disease. It can end in liver failure.

Associated Conditions

- Keratoconjunctivitis sicca
- Renal tubular acidosis
- Peripheral neuropathy
- Autoimmune thyroiditis

- Grave's disease
- Ulcerative colitis
- Rheumatoid arthritis

Type 2 autoimmune hepatitis occurs most commonly in children. Presentation is usually acute or fulminant type, with rapid progression to severe liver disease and cirrhosis. It is associated with autoimmune thyroid disease, insulin-dependent diabetes mellitus and vitiligo.

Type 3 autoimmune hepatitis has clinical features similar to type 1 disease.

Diagnosis

Liver biopsy is the most important diagnostic test.

Indications for biopsy:

- Raised transaminases if relevant serum auto-antibody markers are detected (antinuclear-homogeneous pattern and smooth muscle antibodies in type 1, anti-liver-kidney microsomal antibodies in type 2, and antisoluble liver antigen in type 3).

  Various autoantibodies depending on type:

  Type 1 autoimmune hepatitis: Antinuclear antibody

  Type 2 autoimmune hepatitis: Anti-LKM1 (liver kidney microsomes) antibody, Antinuclear antibody absent.

  Type 3 autoimmune hepatitis: Antibody to soluble liver antigen.

  Antinuclear antibody and Anti-LKM1 antibody absent.
- A florid acute presentation (resembling acute viral hepatitis) if there are no other diagnostic markers.
- Persistently elevated transaminases (above twice normal levels) of uncertain cause.

Other laboratory findings—Non-organ-specific autoantibodies are a cardinal feature of autoimmune hepatitis. Serological testing for anti-LKM1 and anti-SLA/LP is important, because these are subtypes that respond to treatment with immunosuppressive therapy.

Treatment

Prednisone initiated at dose of 60 mg/d.

This high dose is tapered successively over the course of a month down to a maintenance level of 20 mg/d.

An alternative approach is to begin with half the prednisone dose (30 mg/d) along with azathioprine (50 mg/d) then taper prednisone to 10 mg/d. It reduces chances of complications of long term steroid therapy.

PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis (PBC) is a chronic, progressive cholestatic disease of unknown aetiology that affects mainly women. There is a strong association with antimitochondrial antibodies (AMA) and the disease is characterized by granulomatous cholangitis, which leads to progressive destruction of the small and middle-sized intrahepatic bile ducts, leading to fibrosis and cirrhosis.

Clinical Features and Course

Presymptomatic—In this stage, AMA are detectable in the serum but no symptoms and normal LFTs.

Asymptomatic—Circulating AMA and abnormal liver tests, but no characteristic symptoms of PBC. However 50% have established cirrhosis at time of diagnosis.

Symptomatic—Progressive jaundice, patient acquires bottle green colour

- Hepatosplenomegaly
- Finger clubbing
- Malabsorption—Vitamin A (night blindness), vitamin D (hepatic osteodystrophy), vitamin E (Dermatitis), vitamin K (Easybruising, ecchymosis).
- Hypercholesterolaemia—Xanthelasma around the eyes. Xanthomas over joints, tendons, handcreases, elbows and knees.
- CREST syndrome—Calcinosis (Raynaud's phenomenon, sclerodactyly, telangiectasia)

Decompensated patients present with symptoms or signs of liver decompensation (variceal hemorrhage, jaundice, ascites). Median time of death is 3–5 years.

Diseases Associated with PBC

Common (up to 80%)

Sicca syndrome

Less common (about 20%)

Thyroid disease

Arthralgia

Fibrosing alveolitis

Investigations

LFTs—Cholestatic pattern with elevated serum alkaline phosphatase and glutamyltransferase. Serum immunoglobulins, particularly IGM elevated.

Autoantibodies—AMA and nuclear pore protein (gp210) are specific to PBC.

Liver histology—Stages: 1. Granulomatous cholangitis. 2. Inflammation spreading beyond portal tracts, disappearing bile duct syndrome begins. 3. Scarring stage, adjacent portal tracts linked by fibrous septa. 4. Cirrhosis.

Management

No dietary restrictions unless indicated (e.g. sodium restriction for ascites).

Treatment of Symptoms

(a) *Pruritus*—Cholestyramine 4 g t.d.s. If not effective, colestipol. Alternative therapies include rifampicin 300mg/day, naltrexone 25 mg/day, plasmapheresis and a liver support device (e.g. MARS machine), and in severe cases liver transplantation. (b) *Bone disease*—Osteopenia is common and is treated with calcium and bisphosphonates or hormone replacement therapy. (c) *Malabsorption of fat soluble vitamins*—Replacement therapy with vitamins A, D, E and K.

Medical Treatment

Ursodeoxycholic acid (UDCA) 10–15 mg/kg/day in 2–4 divided doses. Reduction in serum alkaline phosphatase within 6 months is a useful predictor of clinical response. It improves both biochemical and histological profile of disease.

Liver transplantation—Indications: Symptomatic disease, intractable pruritus and other features suggesting end-stage liver disease.

SECONDARY BILIARY CIRRHOSIS

It results from prolonged obstruction to large biliary ducts by stones, bile duct strictures or sclerosing cholangitis.

Cl. Fs.: Recurring abdominal pain, fluctuating jaundice if stones, previous history of abdominal surgery in case of stricture.

Investigations: Hyperbilirubinemia, raised serum alkaline phosphatase. Ultrasound and CT scan abdomen, ERCP or MRCP.

Tr.: Relief of strictures by ERCP or surgery.

PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a cholestatic liver disease caused by diffuse inflammation and fibrosis that can involve the entire biliary tree ultimately leading to biliary cirrhosis, portal hypertension and hepatic failure.

Aetiology

Cause is unknown but there is a close association with ulcerative colitis. Evidence suggests that it is an immunologically mediated disease, probably triggered in genetically susceptible individuals by acquired toxic or infectious agents, which may gain entry through the leaky diseased colon.

Clinical Features

Fatigue, intermittent jaundice, weight loss, right upper quadrant abdominal pain and pruritus. Hepatomegaly/splenomegaly and jaundice are common findings. Over 50% patients have ulcerative colitis.

Laboratory Investigations

Serum biochemical tests usually indicate cholestasis. IgM concentrations are increased in about 50%. Sixty-five percent patients are positive for perinuclear antineutrophil antibody.

Diagnosis

Radiology—ERCP shows multiple irregular structuring and dilation. Magnetic resonance cholangiopancreatography is a non-invasive method of imaging the biliary tree.

Histology—Early features are periductal 'onion-skin' fibrosis and inflammation with portal oedema and bile ductal proliferation. Later fibrosis spreads leading to biliary cirrhosis.

Association with other diseases—UC, Crohn's colitis, chronic pancreatitis, retroperitoneal fibrosis, Riedel's thyroiditis, retro-orbital tumors, immunodeficiency states, Sjögren's syndrome, angioimmunoplastic lymphadenopathy, histiocytosis X, autoimmune hemolytic anaemia.

Management

Treatment of cholestasis—Cholestyramine, dose increased until relief.

Management of complications—Broad spectrum antibiotics for acute attack. If obstruction to hepatic bile ducts, balloon dilatation at ERCP. Cholangiocarcinoma is most dreaded complication (Fig. 1).

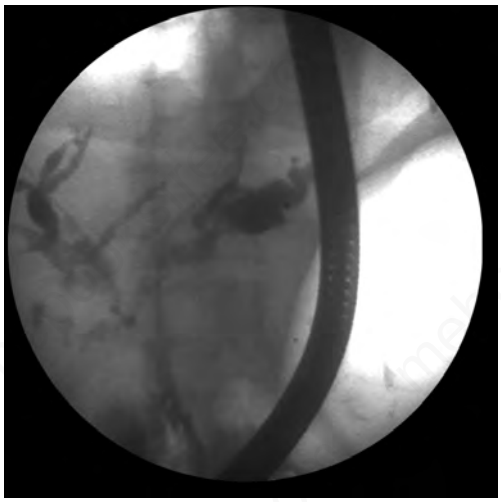


Fig. 1: The ERCP images shows a dilated irregular common bile duct with multiple irregular filling defects. There is also a focal area of stricture involving the right main hepatic duct as well as narrowing and irregularity of the common hepatic duct

Specific treatment—UDCA 20–25 mg/kg daily. Combination therapy with immunosuppressive agents may be useful.

Orthotopic transplantation in young patients with advanced liver disease. Development of Cholangiocarcinoma is relative contraindication of liver transplantation.

4. METABOLIC LIVER DISEASE

NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic Steatohepatitis (NASH) represents only a part of a wide spectrum of non-alcoholic fatty liver disease (NAFLD). Obesity, diabetes, hyperlipidaemia and female sex are important risk factors. NAFLD ranges from simple steatosis and steatohepatitis to advanced fibrosis and cirrhosis and primary liver cancer. Fibrosis is a dynamic process with continuous matrix deposition and matrix removal. Fibrosis to a large extent is produced by activated hepatic stellate cells (HSE). It is important to detect fibrosis in patients with NASH as patients with fibrosis (rather than with necroinflammation alone) may progress to cirrhosis. If NAFLD related cirrhosis develops annual incidence of primary liver cancer is 1%.

Pathophysiological Basis of Hepatic Steatosis

Table 16 gives the pathophysiological basis of hepatic steatosis.

Clinical Features and Diagnosis

Most patients with NASH have few symptoms and no signs of liver disease.

Table 16: Pathophysiological basis of hepatic steatosis

• Increased delivery of fatty acids to liver
– Obesity
– Starvation
• Increased synthesis of fatty acids in liver
– Excess carbohydrate
• Increased mitochondrial beta-oxidation of fatty acids
– Creatinine deficiency
– Mitochondrial dysfunction
• Decreased incorporation of triglycerides into functional VLDL
• Impaired lipoprotein synthesis
• Impaired cholesterol esterification
– Choline deficiency
– Protein malnutrition
• Insulin resistance
– Increased lipolysis
– Hyperinsulinaemia

Diagnosis of NAFLD relies on:

(a) Exclusion of other liver diseases by conventional tests.

(b) Demonstration of widespread fat in the liver by ultrasonography or liver fat quantification.

(c) Persistent cryptogenic elevation of ALT and glutamyltransferase.

(d) Transient elastography (FibroScan) measures liver stiffness used as surrogate marker of fibrosis.

(e) Keratins 8 and 18 (K8/18) are epithelial cytoskeletal proteins, released into the blood as hepatocytes die and studies suggest that serum levels of K8/18 differentiate individuals with NASH from those with simple steatosis or normal livers more reliably than do serum aminotransferase levels. K8/18 levels appear to parallel the severity of liver fibrosis.

Testing for K8/18 has not yet become standard clinical practice.

Management

Aims at reversal of causal factors namely weight reduction, lowering of serum lipids, exercise (improves insulin resistance) and medication to improve insulin resistance.

Fatty Liver

Fatty liver may be macrovesicular or microvesicular (Table 17).

Besides alcohol abuse, fatty liver is observed in obesity, DM (type 2), hypertriglyceridemia, HCV infection, Wilson's disease malnutrition total parenteral nutrition, jejunoileal bypass, rapid weight loss, drugs like corticosteroids, oestrogens, tamoxifen, amiodarone.

Table 17: Macrovesicular vs microvesicular fatty liver

	Macrovesicular	*Microvesicular*
Prevalence	Common	Uncommon
Nucleus	Large droplet pushes nucleus to one side	Small droplet with nucleus in centre
Causes	Alcohol, Obesity,	Fatty liver of pregnancy,
	Diabetes mellitus, Hypertriglyceridemia, Total parenteral nutrition,	Reye's syndrome, Valproic acid, Tetracycline,
	Malnutrition	Jejunoileal bypass
Computed tomography (CT)	Enlarged liver Diagnostic	May not be enlarged Not accurate
Mortality	Low	High

Table 18: Causes of iron overload
Primary iron overload
• Hereditary haemochromatosis
• Congenital aceruloplasminaemia
• Congenital atransferinaemia
Secondary iron overload
• Parenteral iron loading (blood transfusion, iron dextran infusions, chronic haemodialysis)
• Iron-loading anaemia (thalassaemia, sideroblastic anaemia, pyruvate kinase deficiency)
• Post-portacaval anastomosis
• Prolonged oral iron therapy
Complex iron overload
• Juvenile hemochromatosis
• Neonatal hemochromatosis
• Alcoholic liver disease
• Porphyria cutanea tarda
• Bantu siderosis

Table 19: Clinical features of haemochromatosis
• Skin pigmentation
• Liver failure
• Fibrosis leads to cirrhosis with risk of hepatocellular carcinoma
• Maturity onset diabetes mellitus
• Arthropathy (commonly affects MCPs, wrists and knees and may be complicated by chondrocalcinosis and pseudogout)
• Cardiac failure or cardiac dysrhythmias
• Anterior pituitary dysfunction (loss of libido may antedate other clinical manifestations)
• Testicular atrophy

HAEMOCHROMATOSIS

Haemochromatosis is caused by increased iron load in body. Table 18 gives causes of increased iron load in body.

Clinical Features

Haemochromatosis is usually asymptomatic in early stages, but as iron deposition progresses, end-organ damage may lead varied features listed in Table 19.

Juvenile hemochromatosis presents in second decade and in contrast to HCC commonly presents with cardiac failure.

Investigations

(a) *Primary test:* Serum ferritin >400 mg/L in men.
(b) *Supportive test:* Iron saturation> 55%.
(c) *Definitive test:* C282Y, H63D homozygosity.
(d) *Liver biopsy* useful to confirm diagnosis, and measurement of dry-weight liver iron (>1.9 in 90%) (dry-weight liver iron- mcg/gm in homozygotes asymptomatic hemochromatosis 2000–4000 and in symptomatic hemochromatosis 6000–1800).
(e) *LFTs* for assessing hepatic damage (but not presence of disease).

Management

Phlebotomy of 500 mL of blood (200–250 mg iron) once or twice per week until serum ferritin is <50 mg/L; this is maintained by phlebotomy every few months. Anaemia or cardiovascular compromise is managed by removing smaller volumes of blood or by increasing the interval between phlebotomies.

Iron chelating agent deferoxamine can be used. Disadvantage: (1) need to be used parenterally (2) amount of iron removed is 10–20 mg/day which is quite less compared to phlebotomy. Subcutaneous infusion using portable pump is effective method of administration.

Oral iron chelating agent deferasirox is under clinical trial for usage.

End-stage liver disease may be an indication for liver transplantation.

WILSON'S DISEASE

Wilson's disease is an inherited disorder of hepatic copper deposition caused by mutations in the gene *ATP7B* on chromosome 13; pattern of inheritance is autosomal recessive.

Pathophysiology

In Wilson's disease copper is not incorporated into ceruloplasmin within hepatocytes and is not excreted into bile. The level of ceruloplasmin is lower than normal, and because ceruloplasmin contains most of the copper in blood, serum copper levels are low. In addition because copper is not excreted from the liver via the bile, it accumulates in hepatocytes. When hepatocellular storage capacity is exceeded, free copper is liberated into the blood and deposited in various organs, notably the brain, eyes and kidneys. Rarely massive release of copper occurs, leading to acute liver failure, extensive intravascular haemolysis and renal dysfunction.

Table 20: Clinical features of Wilson's disease

Hepatic
• Asymptomatic hepatomegaly
• Persistently elevated AST, ALT
• Fatty liver
• Acute hepatitis resembling autoimmune hepatitis
• Decompensated chronic liver disease
• Fulminant hepatic failure
Neurological
• Movement disorders (tremors, poor coordination, loss of fine motor control, cramped handwriting, choreic/choreoathetoid movements with dystonia)
• Rigid dystonia (mask-like facies, rigidity, gait disturbance, pseudobulbar symptoms such as dysarthria, drooling, difficulty in swallowing)
Psychiatric
• Depression
• Neurotic behaviour
• Aggressive/antisocial behaviour
• Emotional lability
• Impulsive behaviour
• Poor memory and/or difficulty in abstract thinking
Eyes
• Kayser-Fleischer ring*
Other organs
• Pancreatitis
• Arthropathy
• Mild haemolysis, ± transient jaundice
• Kidney (renal tubular damage)
• Infertility or repeated spontaneous abortion
• Hypoparathyroidism

*A characteristic golden brown ring around the periphery of cornea due to deposition of copper in the Descemet's membrane of cornea. Visible at times to the naked eye its presence should be confirmed by slit-lamp examination. It tends to disappear with treatment.

Clinical Features

Spectrum of disease in childhood and early adolescence hepatic disease predominates, in late adolescence neuropsychiatric features predominate. *See* Table 20 for clinical features.

Diagnosis

(a) Primary test: Ceruloplasmin <10 mg/L.

(b) Supportive test: Urine/serum copper >80 mg/24 h.

Table 21: Treatment of Wilson's disease

Disease status	*First Choice*	*Second choice*
Initial hepatitis or cirrhosis without decompensation	Zinc	Trientine
Hepatic decompensation		
Mild	Trientine and Zinc	Penicillaminne and Zinc
Moderate	Trientine and Zinc	Liver transplant
Severe	Trientine and Zinc	Liver transplant
Initial neurologic/ psychiatric	Tetrathiomolybdate and Zinc	Zinc
Maintenance	Zinc	Trientine
Presymptomatic	Zinc	Trientine
Pediatric	Zinc	Trientine
Pregnant	Zinc	Trientine

(c) Definitive test: Liver biopsy with quantitative copper >200 µg/g dry weight.

Management

Treatment is life-long

- *Avoidance of alcohol and major sources of dietary copper*
- **Drugs**

D-penicillamine. About one-third of patients have to change to a different chelator because of side effects including skin disorders, protein-losing nephropathy, lupus-like systemic inflammatory conditions and bone marrow suppression.

Trientine is an alternative to penicillamine, it has fewer adverse effects.

Zinc 50 mg t.d.s. depletes total body copper stores by inducing enterocyte metallothionein, which binds copper avidly. Gastritis is occasionally a problem.

Vitamin E is a useful adjuvant therapy.

Treatment is summarised in Table 21.

The anticopper effects of trientine and penicillamine can be monitored by following 24-h "free" serum copper levels.

Liver transplantation is indicated in patients with fulminant hepatic failure or liver disease unresponsive to standard treatment.

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin is an enzyme α1 globulinproduced by the liver. It's an acute phase reaction and is released in

response to acute inflammation. Its deficiency is associated with liver disease and emphysema. There are multiple variants. The variant is expressed as an allele from both parents. Therefore, a person may have one or two forms of α-1 antitrypsin in the blood. One variant called Z, because of its unique electrophoretic mobility on gel, is the product of a single amino acid gene mutation from the wild type protein (m). The Z protein is difficult to excrete from the liver cell and causes local damage that may result in hepatitis and cirrhosis.

Clinical Features

(a) In neonates α_1-AT deficiency produces cholestatic jaundice.

(b) In adults manifestations are
- Chronic hepatitis
- Cirrhosis
- Hepatocellular carcinoma
- Emphysema
- Chronic bronchitis
- Others - Colitis, pancreatitis, glomerulonephritis

Diagnosis

(a) Serum protein electrophoresis - Absence of α_1-globulin peak.

(b) Low plasma α_1-AT concentration (normal 150 gm/dL).

(c) Liver biopsy – shows α_1-AT containing globules in the liver.

Treatment

(a) No smoking, alcohol.

(b) In pts older than 18 years with airway obstruction, α_1-AT derived from pooled human plasma given IV.

(c) Transplantation of liver or lung.

5. HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a reversible state of impaired cognitive function or altered consciousness. It may complicate acute or chronic liver disease. Two abnormalities hepatocellular failure and portosystemic shunting tend to be present in those in whom encephalopathy develops.

PATHOGENESIS

Hepatic encephalopathy arises as a result of a gut-derived neurotoxin that bypasses the liver to gain access to the CNS, crossing an abnormal blood-brain barrier. It appears that ammonia and other substances trigger a cascade of events in the CNS, the combination of which produces hepatic encephalopathy.

Ammonia hypothesis—Ammonia might exert its effect on the glutamine-glutamate cycle. Glutamate is an important excitatory neurotransmitter; after reacting with post-synaptic receptors, it is converted within astrocytes to glutamine by glutamine synthetase. In hepatic encephalopathy, cerebral glutamate levels are decreased, glutamate reuptake mechanisms are abnormal. Increased glutamine in astrocytes causes osmotic stress leading to cellular swelling.

γ-aminobutyric adrenergic benzodiazepine receptor hypothesis—γ-aminobutyric acid (GABA), benzodiazepine receptor antagonists and neurosteroid may trigger hyperpolarization and subsequent inhibitory effects. Ammonia has an enhancing effect on these stimuli.

Branched-chain amino acid/aromatic amine and false neurotransmitter theory—The branched-chain amino acid: aromatic amino ratio is altered in hepatic encephalopathy. Aromatic amines like tryptophan gain access to the brain and promote production of false neurotransmitters such as serotonin which affects consciousness and the sleep-wake pattern.

Other contributing substances are short-chain and long-chain fatty acids, and mercaptan acting as false neurotransmitters.

Altered glioneuronal communication as a result of low grade astrocyte swelling is one of the terminal events in pathogenesis of HE.

CLINICAL CLASSIFICATION

Although hepatic encephalopathy has a wide range of manifestations, it is important to differentiate between the two common types, which differ in prognosis, severity, pathophysiology and management. In acute liver failure, the shorter the interval between jaundice and encephalopathy, then it is more likely that cerebral oedema may be a major cause of death if fulminant hepatic failure is to occur.

CLINICAL FEATURES

- Altered consciousness (abnormal sleep pattern, drowsiness or coma)
- Monotonous speech
- Intellectual disturbances and behaviour changes
- Asterixis
- Fetor hepaticus
- Decerebrate posturing

Table 22: Precipitating causes of hepatic encephalopathy

• Upper gastrointestinal bleeding
• Electrolyte imbalance (hypokalaemia, metabolic acidosis) Diuresis Vomiting Diarrhoea
• Infection
• Spontaneous bacterial peritonitis Urinary Chest
• Drugs Sedatives Alcohol withdrawal
• Constipation
• Ingestion of a large protein meal
• Paracentesis
• Acute liver injury
• Creation of portocaval shunts (e.g portosystemic surgery, transjugular intrahepatic portosystemic stent shunt)
• Kidney failure
• Trauma

Clinical Types

- In acute liver failure, the shorter the interval between jaundice and encephalopathy, cerebral oedema is likely to occur.
- Encephalopathy complicating cirrhosis and portosystemic shunt develops as a result of a specific precipitating cause or a deterioration of liver function which results in acute, subclinical or chronic encephalopathy but is almost never complicated by cerebral oedema.

PRECIPITATING CAUSES

Precipitating causes of hepatic encephalopathy are listed in Table 22.

Criteria for grading mental symptoms in hepatic encephalopathy is given in Table 23.

INVESTIGATIONS

Laboratory tests: Full blood count, urea, creatinine, sodium, potassium, calcium, glucose and liver function tests. Blood ammonia.

Abdominal paracentesis to exclude spontaneous bacterial peritonitis.

Ultrasonography to exclude thrombosed portal vein and hepatoma.

EEG: Classically shows bilateral, synchronous slowing of frequency from alpha to theta (4–7 Hz) or even to the delta range (< 4 Hz), but these abnormalities are not specific for encephalopathy.

Table 23: Grading of hepatic encephalopathy

• Grade 0	No abnormality detected
• Grade 1	Trivial lack of awareness, euphoria, anxiety
	Reduced attention span
	Impaired performance in addition or subtraction
	Altered sleep rhythm
• Grade 2	Lethargy, apathy, disorientation for time and place
	Obvious personality change
	Inappropriate behaviour
	Dyspraxia and asterixis
• Grade 3	Somnolence to semi-stupor, but responsive to stimuli
	Confusion
	Gross disorientation
	Bizarre behaviour
• Grade 4	Coma

Table 24: Management principles of hepatic encephalopathy

Identification and correction of precipitant
Stop diuretics
Empty bowel of nitrogen content
Control bleeding
Protein-free diet
Drugs (*see* Table 25)
Reversal or reduction of artificially created shunt (particularly TIPS)
Liver transplantation

MANAGEMENT

Management principles of hepatic encephalopathy are given in Table 24.

MINIMAL HEPATIC ENCEPHALOPATHY

Minimal hepatic encephalopathy (MHE) is a condition in which patients with cirrhosis of liver that has normal mental and neurological states on standard clinical examination exhibit a number of neuropsychiatric and neurophysiological defects and may progress to HE.

Pathogenesis

Ammonia-induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease of glucose utilization of various cortical regions that correlate with the patients cognitive functions.

Table 25: Drugs for the treatment of hepatic encephalopathy

Drug	*Dose*	*Comments*	*Adverse-effects*
Ammonia hypothesis			
Disaccharides			
Lactulose	15–30 mL po tds or qds. 300 mL enema plus water 700 mL or 20% lactulose (total 1 L) tds.	Aim for 2–3 stools/d. Enema if pt. comatose or has ileus, or it cannot be given. Reduces colonic-pH and accelerates GI transit.	Bloating, diarrhoea and dehydration if overdose
Lactitol	0.3–0.5 g/kg/d po 20% lactitol (total 1 L) enema bd or tds	As effective as lactulose	Bitter tastes, less side effects
Antibiotics			
Neomycin	2–4 g/d in divided doses	Maximum 48 hours Alters gut flora	Long-term use can cause nephrotoxicity and ototoxicity
Metronidazole	500–800 mg/d in divided doses	Metabolism impaired in liver disease	GI disturbance
Vancomycin	100 mg po bd	Safe in renal insufficiency	
Rifaximin	550 mg BD		Peripheral neuropathy
Combined disaccharide and neomycin			
Lactulose and neomycin		Additive anti-encephalopathic effect. Both reduce absorption of intestinally derived toxins.	Neomycin potentially nephrotoxic
Sodium benzoate	5 g po bd	Increases ammonia excretion	Nausea/vomiting, abdominal discomfort
Ornithine aspartate	20 g iv in 250 mL 5% fructose od	Increases ammonia excretion	Nausea, vomiting
Gamma-aminobutyric acid / benzodiazepine receptor complex			
Flumazenil	1–2 mg bolus iv	May be effective in benzodiazepine-induced hepatic encephalopathy	Flushing, nausea, vomiting, irritability
False neurotransmitters / dopaminergic neurotransmission			
Branched-chain amino acids	1–1.2g/kg/d po	Protein supplement in patients with protein intolerance No clear beneficial effect	
Bromocriptine	PO	No clear beneficial effect	
L-dopa	PO		
Other agents			
Zinc	600 mg/d po	Zinc is a component of urea cycle enzymes, and deficiency is common in cirrhosis	

Diagnosis

(a) Psychometric tests.

(b) Neurophysiological, e.g. EEG, evoked potentials, Critical Flicker Frequency (CFF) and MR spectroscopy.

Management

(a) Branched chain amino acids (BCAAs) may improve nitrogen metabolism, blood ammonia level and psychomotor tests.

(b) L-ornithine L-aspartate (OA) exerts its ammonia lowering action on kidneys, skeletal muscles, brain and also the liver.

(c) Lactulose lowers ammonia levels by alteration in gut flora, lowers colonic pH and decreases absorption of ammonia by non-ionic diffusion.

(d) Probiotics.

6. ACUTE LIVER FAILURE

Acute liver failure is defined as evidence of coagulation abnormality, usually an International Normalized Ratio (INR) ≥1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of <26 weeks duration.

Table 26: Causes of acute liver failure
Viral hepatitis
Viral hepatitis A, B, D and E
Drugs and toxins
Predictable
Paracetamol
Mushrooms
Carbon tetrachloride
Zinc phosphide (rat killer)
Idiosyncratic
Anti-TB drugs (isoniazid, rifampicin)
Sulphonamides
NSAIDs (diclofenac)
Ketoconazole
Tricyclic antidepressants
Anti-epileptics (sodium valproate, carbamazepine, phenytoin)
Flutamide
Miscellaneous
Wilson's disease
Pregnancy-related syndromes
Budd-Chiari syndrome
Lymphoma
Sepsis
Hyperthermia
Hepatic ischaemia

CLASSIFICATION

- Hyperacute—Jaundice (Illness) for <7 days before onset of encephalopathy (e.g. paracetamol poisoning)
- Acute—Jaundice (Illness) for 8–28 days (7–21 days) before onset
- Subacute—Jaundice (Illness) for 4–12 weeks (21 days to 26 weeks) before onset

CAUSES

Table 26 enumerates causes of acute liver failure. Hepatitis B is the most common cause with or without hepatitis D. Hepatitis E is most lethal in pregnant women.

CLINICAL FEATURES

Encephalopathy—It is the usual presentation. Hypoglycaemia may impair consciousness before onset of encephalopathy.

Other signs of liver dysfunction—Flappy tremor and encephalopathy following acute liver failure ranges from mild drowsiness to complete unresponsiveness. Fetor is usually absent. Because of rapid onset, patients with hyperacute liver failure may not be overtly jaundiced.

Involvement of other systems

- CVS Hypertension (with cerebral oedema)
  Hypotension
  Tachyarrhythmias
  Bradycardia
- Fever—Due to liver necrosis or infection
- Kidney failure—Early with paracetamol overdose, at later stage in other etiologies
- Respiratory failure—Mainly due to infection, fluid overload and adult respiratory distress syndrome, but aspiration and pulmonary hemorrhage may contribute.
- Coagulopathy—May manifest as bleeding from puncture sites and urinary and GI tracts.

INVESTIGATIONS

Tests for infection—Blood screened for acute hepatitis A and B by testing for anti-HAV IgM and anti-HBc IgM respectively. Also herpes simplex serology. HIV serology testing.

Toxicology screen, drug history, autoimmune markers (ANA and ASMA levels), ceruloplasmin level (if patient age is <40 years).

Ultrasonography and CT—For patency of hepatic veins, malignant infiltration and estimate of liver volume.

Prothrombin time and serum bilirubin, aminotransferase levels, serum albumin, serum creatinine, electrolyte levels.

MANAGEMENT

Drugs—(a) N-acetylcysteine is the only drug with a proven role. Its metabolism produces glutathione which detoxifies the toxic molecule. (b) Sucralfate to reduce bleeding from gastric erosions. (c) Vitamin K parenterally to patients who have been jaundiced for more than 2 weeks.

Inotropic support—Combination of noradrenalin or dopamine with N-acetylcysteine or prostacyclin.

Treatment of complications:
Table 27 summarises treatment of complications.

Liver transplantation—It has a survival rate of more than 60%. Auxiliary liver transplantation for a subgroup of patients who have the capacity to regain normal function in the native liver.

Other techniques—Extracorporeal circuits incorporating viable hepatocytes to offer artificial liver support. These devices aid recovery by acting as a bridge to transplantation, with or without a preliminary hepatectomy which often temporarily stabilises critically ill patients.

Table 27: Treatment of complications

Complication	*Management*
Intracranial hypertension and neurohypoxaemia	Intensive monitoring Minimize auditory and tactile stimuli
Subclinical seizures	Mannitol, barbiturates, inotropes, hyperoxygenation
Kidney failure	Continuous hemofiltration
Infection	Intensive treatment with systemic antimicrobials
Hypotension	Vasopressors with N-acetylcysteine or prostacyclin
Hypoglycaemia	Hourly blood glucose estimations
Respiratory failure	Early ventilatory support NO inhalation in severe cases
Coagulopathy	Treat clinical coagulopathy Platelet count to be watched
Pancreatitis	High index of suspicion required May contraindicate transplantation if severe
Malnutrition	Parenteral feeding
Electrolyte abnormalities	Tr. of sodium, potassium, phosphate, magnesium deficiency
Acid-base abnormalities	Metabolic alkalosis dominates (except in paracetamol poisoning)

7. JAUNDICE

It is a symptom complex characterized by increase of bile pigments in body fluids and tissues. Jaundice is perceptible only when the level of bilirubin and its conjugates exceeds 1.5 mg per 100 mL plasma. In its mildest form it is recognized by yellow discolouration of sclera. With deeper jaundice the skin and mucous membrane are also stained.

NORMAL BILIRUBIN METABOLISM (FIG. 2)

1. *Breakdown phase*—Haemoglobin breakdown occurs in the reticuloendothelial system forming the bile pigment bilirubin which is transported in the blood stream attached to albumin.
2. *Conjugation phase*—Unconjugated bilirubin is conjugated by the endoplasmic reticulum enzyme of the hepatocytes glucuronyl transferase, into bilirubin mono- and diglucuronide. These bilirubin conjugates are water soluble and transported into the bile via specific carriers on the hepatocyte membrane. Deep jaundice is always predominantly conjugated.

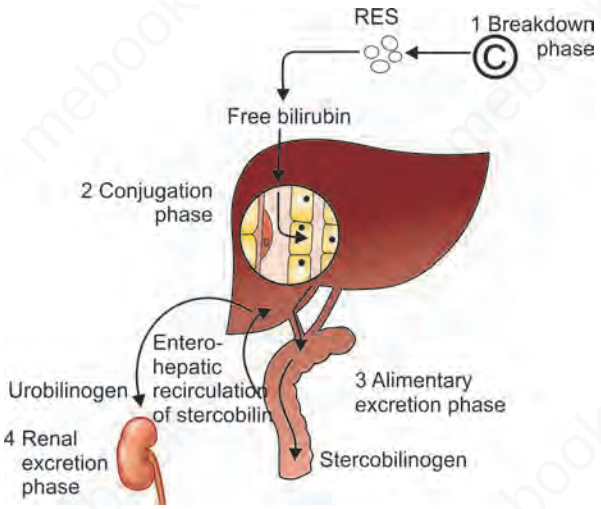


Fig. 2: Normal bilirubin metabolism

3. *Alimentary excretion phase*—The bilirubin is excreted through the bile canaliculi and so reaches the intestines, where it is converted into stercobilinogen, by bacterial action. A large part is reabsorbed from the intestine into portal blood and carried back to the liver and re-excreted into the bile (enterohepatic circulation of bile pigments). Stercobilinogen which is not absorbed is excreted in the stool.

TYPES OF JAUNDICE

Jaundice is best sub- divided into unconjugated and conjugated types. Deep jaundice is always predominantly conjugated.

Causes of Unconjugated Jaundice

- *Increased bilirubin production results* from any form of haemolysis whether congenital, e.g. hereditary spherocytosis sometimes termed 'acholuric jaundice' to emphasize absence of bile in urine, or acquired (e.g. malaria).
- *Impaired hepatic uptake of bilirubin:* Drugs are the main cause; they compete for protein binding or for the uptake receptor.
- *Impairment of glucuronyl transferase:* The enzyme that converts bilirubin into a water-soluble glucuronide suitable for excretion into bile is immature in premature babies, and is congenitally absent (type I) or reduced in (type II) Crigler-Najjar syndrome. Isolated mild unconjugated jaundice in absence of liver enzyme abnormalities, almost always results from Gilbert's syndrome.

Table 28: Clinical classification and causes of jaundice

1. ***Hepatocellular jaundice***
Acute:
• Viral hepatitis
• Hepatic immaturity
• Drug hepatitis
• Alcoholic hepatitis
• Leptospirosis
• Infectious mononucleosis
• Yellow fever
Chronic:
• Cirrhosis
• Congenital hyperbilirubinaemias
2. ***Obstructive jaundice***
Without mechanical obstruction:
Acute:
Drugs, e.g. chlorpromazine
Viral hepatitis with cholestasis
Pregnancy (first 3 months)
Chronic:
Primary biliary cirrhosis
With mechanical obstruction:
Intrahepatic:
Intrahepatic neoplasms and reticulosis
Congenital obliteration of bile ducts
Extrahepatic (Surgical jaundice):
Inside duct: Gallstones, foreign body (broken T-tube), parasites (ascaris, hydatid).
In duct wall: Congenital atresia, stricture, tumour of bile duct, sclerosing cholangitis
Outside duct: Carcinoma head of pancreas or ampulla of Vater, metastasis in porta hepatitis, chronic pancreatitis.
3. ***Hemolytic jaundice***

Causes of Conjugated Jaundice

(a) In most cases of acquired liver disease, whether acute hepatitis or cirrhosis, jaundice is predominantly conjugated and accompanied by dark urine.

(b) In most cases cholestasis is the most common pattern of drug-induced jaundice. Common causes of extrahepatic cholestasis are bile duct stones and malignant bile duct obstruction (e.g. pancreatic cancer).

CLINICAL CLASSIFICATION

Three types but combinations can occur (Table 28).

Table 29: Differentiating features between types of jaundice

	Hepatocellular	*Obstructive*	*Hemolytic*
Colour of jaundice	Orange yellow	Greenish yellow	Lemon yellow
Depth of jaundice	Variable	Deep	Mild
Pruritus	Variable	Present	Absent
Bleeding tendency	Present	Present (late)	Absent
Bradycardia	Absent	Present	Absent
Anaemia	Absent	Absent	Present
Splenomegaly	Variable	Absent	Present
Palpable GB	No	May be present	No
Features of hepatocellular failure	Present (early)	Present (late)	Absent

***Hemolytic jaundice*—**Results from increased destruction of RBCs or their precursors in the marrow, causing increased bilirubin production. A healthy liver can excrete a bilirubin level 6 times greater than normal before unconjugated bilirubin accumulates in the blood.

Increased destruction of RBCs or their precursors in the marrow, causing increased bilirubin production (See hemolytic anaemias). A healthy liver can excrete a bilirubin level 6 times greater than normal before unconjugated bilirubin accumulates in the blood.

Table 29 gives differentiating features between types of jaundice.

(a) *Symptoms and signs:*

(i) Anaemia – may vary from time to time developing rapidly with hemolytic crisis.

(ii) Jaundice usually mild and of a lemon yellow tint. No pruritus.

(iii) Pigmented gallstones may be associated with features of chronic cholecystitis.

(iv) Splenomegaly in chronic forms.

(v) Ulcers or pigmentation from healed ulcers usually over the malleoli in some cases.

(b) *Haematology*—Anaemia variable, anisocytosis, stippling, target cells. Reticulocytes increased. Leucocytosis common.

(c) *Stools*—Dark in colour due to increased stercobilinogen.

(d) *Urine*—Urobilinogen increased only during crisis. Haemoglobinuria if rapid blood destruction.

(e) *Serum biochemistry*—Serum unconjugated bilirubin raised (usually 1–3 mg/100 mL serum). Serum conjugated bilirubin slightly raised.

OTHER CAUSES OF JAUNDICE

1. ***Portal cirrhosis***—(a) Jaundice usually slight and transient. (b) Liver enlarged, may be tender. (c) Long history of dyspeptic symptoms. (d) Hematemesis common.
2. ***Amoebic abscess***—(a) History of amoebic dysentery may be obtained. (b) Liver enlarged and tender. Compression tenderness. (c) Jaundice slight. (d) Remittent fever. (e) Excessive sweating. (f) Rapid response to metronidazole or tinidazole.
3. ***Acute alcoholic hepatitis***—History of heavy consumption of alcohol. Anorexia, weight loss, weakness and right upper abdominal pain. Jaundice. Liver enlarged and tender. Spleen may be palpable. Fever and mild anaemia.
4. ***Drug-induced jaundice***—It can be in the form of acute hepatitis, cholestasis or steatosis.
5. ***Autoimmune hepatitis***—It occurs typically in young women who present with jaundice of sudden onset and features of chronic liver disease. Other organs are involved and autoimmune phenomena are associated.
6. ***Infectious mononucleosis***—(a) Jaundice between 5 to 14 days after onset of illness. Mild and transient. (b) Liver seldom palpable. (c) Pyrexia persisting Inspite of subsidence of jaundice. (d) Late glandular enlargement. (e) Typical blood changes. (f) Positive Paul-Bunnell test.
7. Malaria- Jaundice with associated liver dysfunction can be seen in severe cases of *Plasmodium falciparum* malaria. The jaundice in these cases is due to a combination of indirect hyperbiIirubinemia from hemolysis and both cholestatic and hepatocellullar jaundice.

Investigation of a Case of Jaundice

History

Personal History:

Sex:	More in males:	More in females:
	Ca pancreas	Common duct stones
	Liver cirrhosis	Primary biliary cirrhosis
	Hepatoma	Ca gallbladder
Occupation:		Exposure to alcohol
		Infection in medical and paramedical
Sexual association:		Diseases associated with male homosexuality
Family history		Familial tendency in congenital hyperbilirubinemia
		Hemolytic jaundice
		Gallstones
		Family contacts with other jaundiced patients

Past history

- Hepatotoxic drugs
- Blood transfusion
- Renal dialysis
- Alcohol consumption
- Biliary surgery
- Sepsis: pneumonia or urinary tract infection

Duration of jaundice

< 1 month	Viral hepatitis
1–2 months	Autoimmune hepatitis, Carcinoma
> 2 months	Chronic liver disease

Jaundice progression

Progressive	Malignant obstruction
Fluctuating	Stone in common bile duct
	Carcinoma ampulla of Vater
Persistent mild jaundice of varying intensity	Recurrent hemolytic episodes

Symptoms

• Anorexia and weight loss	Malignancy Cirrhosis
• Abdominal pain	
Colicky	Common duct stone Extrahepatic biliary obstruction
Epigastric radiating through back	Acute pancreatitis Ca pancreas Posterior penetrating duodenal ulcer
• Fever	Viral hepatitis Cirrhosis
• Chills and rigor	Acute cholecystitis Cholangitis Amoebic liver abscess
• Pruritus	Obstructive jaundice Intrahepatic cholestasis
• Backache	Pancreatic disease
• Dry eyes/mouth	Sjögren's syndrome (associated with biliary cirrhosis)
• *Colour of stool*	
Clay coloured	Acute viral hepatitis (for few days)
Cholic and acholic alternately	Common duct stone
Acholic persistent	Neoplasm
Brown stools with deep jaundice	Parenchymal jaundice
Tarry stools with jaundice	Ca of ampulla of Vater Ca pancreas invading stomach or duodenum
• *Colour of urine*	
Dark	Cholestasis
Hepatocellular jaundice	

General Physical Examination

Depth of jaundice	
Orange-yellow	Liver cell jaundice
Pale yellow tint	Hemolytic jaundice
Greenish-yellow	Obstructive jaundice
Signs of chronic liver disease	Palmar erythema Clubbing White nails Gynecomastia Dupuytren's contracture
Skin changes	
Vascular spiders	Hepatocellular jaundice
Greyish pigmentation	
Trunk	Biliary cirrhosis
Skin folds	Hemochromatosis
Acneform vesicular rash	Acute viral hepatitis Autoimmune hepatitis

Xanthoma	Long-standing cholestasis Primary biliary cirrhosis (on elbows and palms)
Other rashes	Drug reaction
Purpura	Manifestation of systemic disease possibly cirrhosis
Absent sexual hair	Cirrhosis
Pigmented shins	Congenital spherocytosis
Tumour deposits	Malignancy
Anaemia	Haemolysis Cirrhosis Malignancy
Personality changes	Hepatocellular jaundice
Breath	Faecal odour in liver failure
Conjunctival suffusion	Leptospirosis
Peripheral oedema	Portal hypertension Hypoproteinemia
Features of alcoholism	Parotid enlargement Dupuytren's contracture Gynecomastia Soft testes Fine tremors
Chipmunk facies	Hemolytic anaemia

Local Examination

Abdominal	
Periumbilical veins	Cirrhosis
Liver	
• Size	
Massive	Malignant deposits Obstructive jaundice
Moderate	Hepatitis Cirrhosis Fatty infiltration
• Tenderness	Viral hepatitis Amoebic abscess Alcoholism Bacterial cholangitis Malignancy (rarely)
• Nodularity	Cirrhosis Hepatoma Hepatic syphilis
• Bruit	Primary hepatocellular tumour Alcoholic hepatitis
Gallbladder	
• Nontender palpable	Neoplastic obstruction of bile duct
• Firm or hard	Ca gallbladder

• Not palpable with cholestatic jaundice	Shrunken GB with stone blocking common bile duct (Courvoisier's law) Block in common bile duct above level of cystic duct
Splenomegaly	Hemolytic jaundice Hepatitis acute or chronic Cirrhosis Protracted obstruction of common bile duct by stone or tumour
Abdominal mass	Malignancy
Ascites	Cirrhosis Peritoneal tumour implants Portal obstruction due to tumour
Lymphadenopathy	Infectious mononucleosis Lymphoma Acute lymphoblastic leukaemia Disseminated TB
Xanthomata	Biliary obstruction Biliary cirrhosis

Investigations

White cell count	
Leucopenia	Hepatocellular jaundice
Leucocytosis	Cholangitis, gallstones, carcinomatosis
Eosinophilia	Drug-induced jaundice
Atypical WBCs	Infectious mononucleosis
Urine	
Urobilinogen	
Absent	Common bile duct obstruction
Excess	Hemolytic jaundice, liver cell disease
Bilirubin	
Absent	Hemolytic jaundice
Excess	Obstructive jaundice
Faeces	
Occult blood	Ampullary, pancreatic or alimentary tract Ca or portal hypertension
Viral markers	For viral hepatitis, cytomegalo and Epstein-Barr
Liver function tests	
Hemolytic jaundice	Unconjugated hyperbilirubinaemia No bilirubin in urine Other LFTs usually normal
Liver cell jaundice	Elevated total and conjugated bilirubin Raised serum transaminases Reduced albumin in chronic jaundice
Cholestasis	Raised serum alkaline phosphatase Prolonged PT (corrected by vitamin K)

Indeterminate patterns	Fatty change Cirrhosis Hemochromatosis Autoimmune hepatitis Malignancy
Additional blood tests	
For hemolytic jaundice	Hb and absolute values, reticulocyte count, blood film and immature cells, erythrocyte fragility, Coomb's test, bone marrow examination, transfused red cells survival studies
Immunological tests	(Refer)
Unusual cases of hepatitis	Infectious mononucleosis (Paul-Bunnell) Toxoplasmosis (Toxoplasma dye test) Cytomegalovirus (Cytomegalic complement fixation test)

Radiography

• CXR	May reveal metastasis
• Plain X-ray abdomen	Gallstones
• Barium swallow	Oesophageal varices in cirrhosis
• Barium meal	Widening of C loop of duodenum or displacement of duodenum by pancreatic tumour (inverted 3 sign)

Liver imaging

Ultrasonography	
Dilated bile ducts seen as irregular tortuous tubes with poor wall echoes	Obstructive jaundice (too many tubes sign) Differentiation of 'medical' from 'surgical' jaundice
Common hepatic duct > 4 mm diameter or common bile duct > 7 mm diameter	Denotes obstruction
Intrahepatic bile ducts dilated and GB and extrahepatic biliary tree collapsed	High obstruction
CT scan	
Gallbladder	Gallstones Malignant obstruction
MRCP	Biliary tree Defining tumour margins and metastasis (Fig. 3) and number of lesions. Focal lesions like hydatid cysts, polycystic liver disease, liver abscesses (Fig. 4).
ERCP and PCT	(Refer)
Selective angiography	
Arterial	Pancreatic tumors Liver metastasis Invasion of vessels, tumour vessels and vascular displacement
Venous	Occluded hepatic veins Portal vein imaging

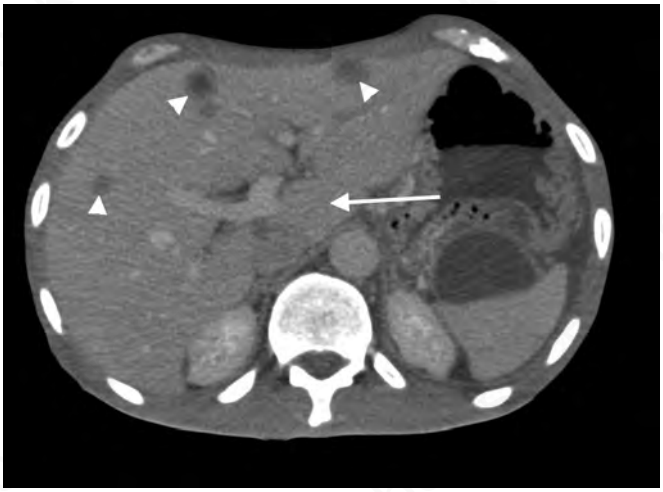


Fig. 3: Abdominal CECT with pancreatic malignancy (long arrows) with metastasis in liver (arrow heads)

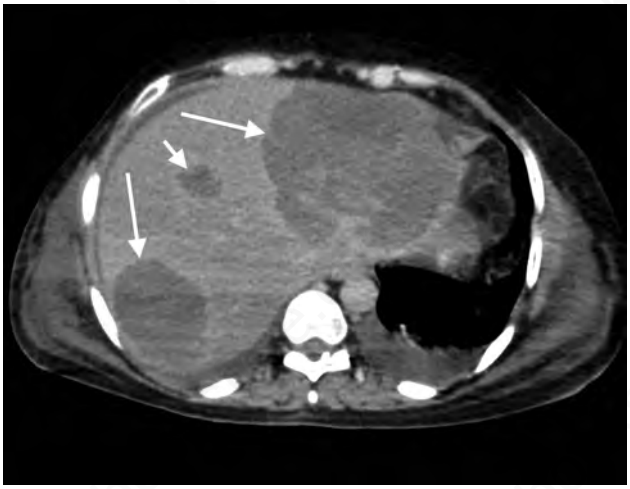


Fig. 4: Abdominal CECT showing multiple hypodense liver abscesses (arrows)

Liver biopsy	Characteristic histology in acute hepatitis, cirrhosis, changes due to obstruction of common bile duct, liver malignancy, drug-induced jaundice.
Endoscopy	
Gastroscopy	Varices
Duodenoscopy and cannulation	Visualization of bile ducts and biliary tree
Laparoscopy	Tumour nodules on liver
	Large GB with dark green liver due to extrahepatic biliary obstruction.
	Hobnail liver in cirrhosis
	Pale yellowish-green liver suggestive of hepatitis
Laparotomy	If extrahepatic cause for cholestasis, or diagnosis is in doubt.

8. CIRRHOSIS OF LIVER

The term cirrhosis is applied to chronic diffuse liver disease of varied aetiology, and characterised by hepatic cell necrosis, proliferation of connective tissue and nodular regeneration, or in other words abnormal reconstruction of lobular architecture, and disturbed hepatic circulation.

PATHOLOGICAL CLASSIFICATION

1. *Micronodular cirrhosis* (portal or alcoholic cirrhosis). Characterised by thick, regular bands of connective tissue, by regenerating small nodules of almost same size and involvement of every lobule of the organ.
2. *Micronodular coarse cirrhosis* (post-necrotic). Liver reduced in size. Nodules of regenerating liver cells of different sizes intersected by fibrous bands of varying thickness containing proliferating bile ducts.
3. *Mixed micronodular and macronodular*—following bile duct stricture and minimal liver cell failure and portal hypertension.

AETIOLOGY OF CIRRHOSIS

Various aetiologies of cirrhosis are listed in Table 30.

Clinical features of cirrhosis depend mainly on:

(a) Liver cell dysfunction
(b) Portal hypertension

Onset

- *Vague* with anorexia, dyspepsia, weight loss, malaise and loss of libido.
- *Dramatic* with jaundice, ascites or haematemesis.
- *Asymptomatic* with hepatomegaly
- *Miscellaneous*—Swelling of ankles, diarrhoea, low grade fever.

Table 30: Aetiologies of cirrhosis

• *Viral hepatitis B and C*
• *Alcohol*
• *Cryptogenic*
• *Metabolic:* Hemochromatosis Wilson's disease α_1-antitrypsin deficiency Cystic fibrosis Glycogen storage disease Galactosaemia
• *Biliary obstruction* Primary biliary cirrhosis Sclerosing cholangitis Secondary biliary cirrhosis
• *Venous outflow obstruction* Budd-Chiari syndrome Veno-occlusive disease Congestive heart failure
• *Drugs* Methotrexate Methyldopa Oxyphenisatin Amiodarone
• *Indian childhood cirrhosis*

Hepatic

- ***Hepatomegaly***—Liver may be palpable, non-tender, shrinks as disease advances.
- ***Jaundice***—Uncommon, when present it may be due to hepatocellular failure or intrahepatic cholestasis.
- ***Ascites***

  Signs of ascites correlated to fluid quantity

  CT scan – 80 mL
  Ultrasound – 100 mL
  Penfield methods – 120 mL
  Puddle sign – 150 mL
  Shifting dullness – 1–1.5 litres
  Horse-shoe shaped dullness – 2–3 litres
  Fluid thrill – > 3 litres

PATHOGENESIS OF ASCITES IN CIRRHOSIS (FIG. 5)

1. *Renal*—Liver failure leads to decrease in renal blood flow which then results in reduction of GFR and resorption of salt and water by renal tubules, thus salt and water retention.
2. *Secondary hyperaldosteronism*—Increased levels of renin which stimulates the angiotensin renal system which then causes secondary hyperaldosteronism causing salt and water retention.
3. *Vasopressin*—Vasopressin cannot be metabolised by liver, hence kidney water output is reduced.
4. *Increased capillary hydrostatic pressure* due to portal hypertension causing localization of fluid within peritoneal cavity.
5. *Reduced plasma osmotic pressure* due to hypoalbuminuria which once again causes extravasation of fluid, ascites and oedema.
6. *Hepatic lymph* oozes out from the surface of cirrhotic liver, this with portal hypertension adds to development of ascites.

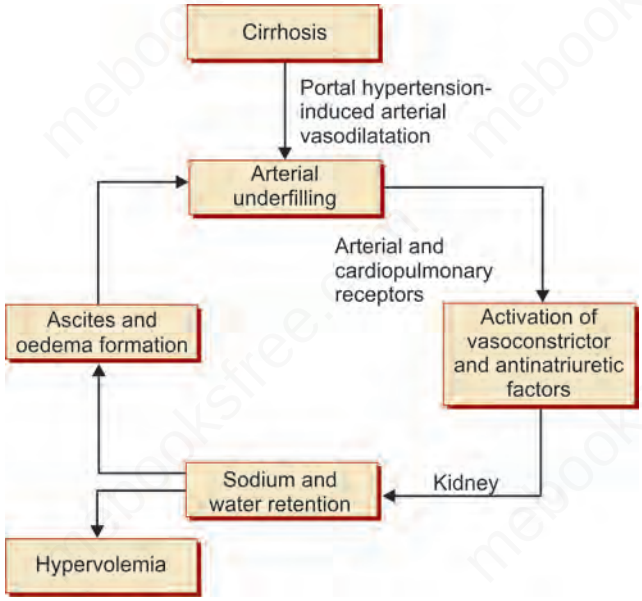


Fig. 5: Ascitis formation in cirrhosis

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Spontaneous bacterial peritonitis is characterized by spontaneous infection of ascitic fluid without any intra-abdominal surgically treatable cause and is a severe complication of ascitic. In adults it occurs frequently in association with cirrhosis of liver, other causes are metastatic malignant diseases, chronic active hepatitis, congestive heart failure, acute viral hepatitis, SLE, lymphedema and in patients with no underlying cause.

The pathogenesis of SBP is bacterial translocation from the gut into mesenteric lymph nodes leading to bacteremia and seeding of ascitic fluid. This is facilitated by a diseased liver and altered portal circulation.

Table 31: Causes of abdominal pain in cirrhosis
TB peritonitis
Spontaneous bacterial peritonitis
Peptic ulcer
Chronic cholecystitis (pigment gallstones)
Portal vein thrombosis
Pancreatitis (with alcoholic cirrhosis)
Hepatoma
Zieve's syndrome (alcoholic) (Acute haemolysis, Acute alcoholic hepatitis, Hyperlipidaemia)

Causes of rapid development of ascites:

1. Decompensating event – GI bleeding or sepsis.
2. Sudden exacerbation of necroinflammatory activity in liver, e.g. seroconversion in a chronic hepatitis B carrier with a 'hepatitis flare'.
3. Alcohol abuse.

CLINICAL FEATURES

Gastrointestinal

- *Haematemesis*—Due to rupture of oesophageal varices
- *Peptic ulcer*
- *Parotid enlargement*
- *Pancreatitis*
- *Chronic cholecystitis*
- *Portal vein thrombosis*
- *Abdominal pain in cirrhosis* (Table 31)

Endocrine

Male—Gynecomastia, testicular atrophy, feminisation, reduced body hair, impotence.

Female—***Lowered libido and usually atrophy of the breasts.***

Haematological

- *Purpura*
- *Anaemia* may be caused by—(i) bleeding, (ii) impaired conversion of folic acid into folinic acid, (iii) impaired metabolism of vitamin B12, (iv) haemolysis and (v) malnutrition.

Dermatological and Musculoskeletal

- *Arterial spiders* (Spider naevi)
- *Palmar erythema* (Liver palms)
- *Alopecia*—Loss of pubic, axillary and facial hair; women may rarely develop masculine distribution of body hair.
- *Nails*—White due to opacity of nail bed. Muehrcke's bands—white transverse bands across the nails if hypoalbuminemia. Clubbing may occur.
- *Paper money skin*—Often associated with arterial spiders and in a similar distribution are numerous small vessels scattered in the skin.
- *Dupuytren's contracture.*
- *Muscle atrophy.*
- *Erythema nodosum.*

Circulatory

- *Hyperdynamic circulation* due to increased blood volume, associated anaemia, A-V shunting within the lungs and excessive vasodilator material due to failure of detoxification by the damaged liver.
- *Clubbing*
- *Cyanosis*

Neurological

- *Porto-systemic encephalopathy*
- *Peripheral neuropathy*

HEPATORENAL SYNDROME

(Functional renal failure)—This azotaemia syndrome is renal failure with normal kidney function in a patient with chronic liver disease. It is due to reduction in effective circulatory volume and renal blood flow and usually affects patients of alcoholic cirrhosis. The kidney is normal histologically and functions normally if transplanted.

Two types are seen

a. Type 1 HRS: Progressive impairment in renal function with rapidity in 1–2 weeks.

b. Type 2 HRS: There is slow deterioration in renal function over 6 months with better outcome than type 1 HRS.

One-third of patients with chronic liver disease have mild hypoxaemia.

Clinical Features

- Ascites common
- Hyponatraemia
- Hepatic encephalopathy
- Lowered BP
- Pronounced oliguria

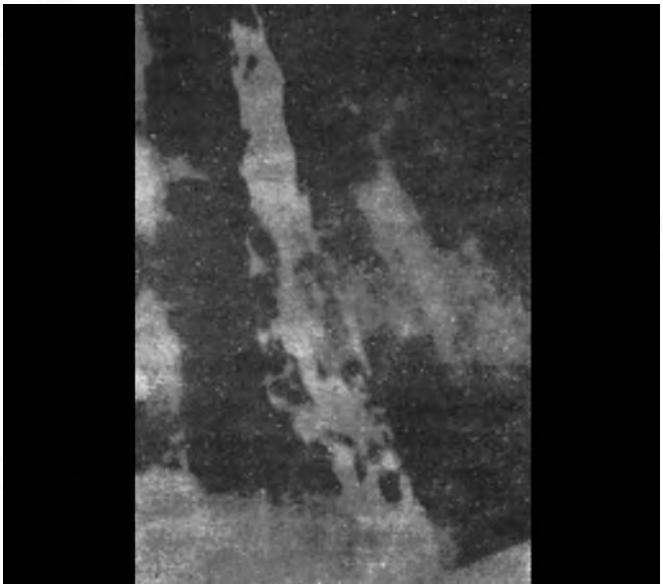


Fig. 6: Oesophageal varices after barium swallow.
Note: Ribbon-like lucent defects and irregular pattern

- Low renal sodium concentration (< 10 mmol/L)
- Urinary protein and casts minimal or absent.

Once kidney failure occurs due to any cause, with a high creatinine level in presence of cirrhosis, mortality is almost 100%. There is no effective treatment except liver transplantation. Haemofiltration or dialysis do not affect the outcome.

HEPATOPULMONARY SYNDROME (HPS)

HPS is defined as a clinical triad of advanced liver disease, arterial deoxygenation and intrapulmonary vascular dilatation. It is a rare complication of liver disease of varies etiology and has poor prognosis. The major clinical manifestations of HPS are cyanosis, clubbing and platypnoea. Arterial hypoxemia and orthodeoxia are specifically present. Hypoxaemia in hepatopulmonary syndrome results from right to left intrapulmonary shunts through dilatation in pulmonary vessels.

Respiratory

- May be cyanosis due to reduced pulmonary O_2 saturation due to intrapulmonary shunting through tiny AV fistulae.
- Reduced diffusing capacity due to ventilation-perfusion mismatch.
- Reduced transfer factor.
- Further reduction in pulmonary function due to raised diaphragm (ascites, hepatomegaly) and pleural effusion.

Miscellaneous

- *Fever*—Low grade common due to bacteraemia, or continuing hepatic cell necrosis, or infected ascites, or rarely due to development of hepatoma.
- *Hydrothorax*—may occur in right pleural cavity.

INVESTIGATIONS IN CIRRHOSIS

1. ***Blood—***(a) Anaemia—Normocytic, normochromic; may be hypochromic if gastric haemorrhage. Occasionally macrocytic. (b) Low white cell count or reduced platelets due to hypersplenism. (c) Raised ESR from abnormal serum protein. (d) Mitochondrial antibodies in biliary cirrhosis.
2. ***Liver function tests***—may be normal in patients with compensated cirrhosis. Usually slight increase in aminotransferase, and immunoglobulin levels and fall in serum albumin. Prothrombin time prolonged and not shortened by vitamin K.
3. ***Radiology:***
   - *Barium swallow*—Oesophageal (Fig. 6) and gastric varices.
4. ***Imaging:***
   - *Ultrasound*—(i) In cirrhosis may cause a 'bright liver' (also in fatty infiltration and chronic hepatitis), and nodules may be seen. (ii) In portal hypertension a large congested spleen is seen with dilatation of splenic and portal veins. (iii) Can also detect very small amounts of ascites.
   - *CT scan*—In early cirrhosis, CT scan is unremarkable, though late in the disease the contour of the shrinking liver is irregular due to nodules, the caudate lobe is enlarged and ascites is invariable (Fig. 7).
   - *Trans-splenic portal venography*—is required if the portal vein needs imaging (prior to shunt), when ultrasound or CT scan have failed to show it or have given conflicting results. It can confirm suspected malignancy.
   - *Selective coeliac arterioportography*—If splenic venography is not possible, selective catheterization of coeliac axis can be performed following percutaneous puncture of femoral artery. The arteriographic phase will show characteristic corkscrew appearance of intrahepatic arteries in cirrhosis.
5. ***Histological:***

   Liver biopsy shows typical changes.

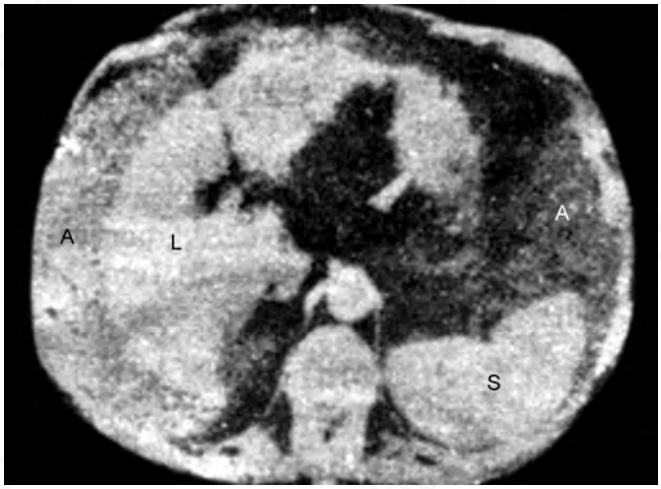


Fig. 7: CT scan in a patient with liver cirrhosis.
Note: Ascitic fluid (A), small irregular liver (L) and spleen (S)

6. ***Scopies:***
   (a) *Proctoscopy*—To visualise hemorrhoids.
   (b) *Endoscopy*—Endoscopic appearance of red areas (cherry red spots) and darkening of the mucosa over the varices suggests that rupture may be imminent.
   (c) *Laparoscopy*—To visualise nodular liver surface. Distended vessels in falciform ligament over the peritoneum may indicate portal hypertension.
7. ***EEG***—In presence of neuropsychiatric changes.

COMPLICATIONS OF CIRRHOSIS

1. ***Due to portal hypertension***– Haematemesis, thrombosis of portal vein.
2. ***Due to liver cell dysfunction*** – Portasystemic encephalopathy.
3. ***Due to formation of regeneration nodules*** – Hepatoma.
4. ***Mechanical due to ascites*** – Hernia – Umbilical, inguinal, femoral, hiatal or incisional.
5. ***Due to infection:***
   (a) *Spontaneous bacterial peritonitis*—occurs due to bacteraemia of ascitic fluid. It may be asymptomatic or give rise to symptoms of abdominal pain, fever, malaise or encephalopathy, or a non-specific feeling of being unwell. There may be a pseudoileus. Ascitic fluid—Neutrophil count > 250 mm^3, usually pure culture of one organism.

Table 32: Differentiating features between postnecrotic and alcoholic cirrhosis of liver

	Postnecrotic cirrhosis	*Alcoholic cirrhosis*
Sex	More common in females	More common in males
Age	Any age	Usually middle age
Previous hepatitis	Frequent	Rare
Liver	Small or normal	Large
Spleen	Usually palpable	Not palpable in about 75%
Ascites	++	+
Haematemesis	Frequent	Uncommon
(Oesophageal varices)		
Hepatic coma	Common	Rare
Pyrexia	Rare	Common
Obesity	Rare	Common
Special features	Nil	Delirium tremens, peripheral neuritis, parotid enlargement,
		Dupuytren's contracture.
		Wasting of muscle mass.
		Increase in α-glutamyl transferase, MCV or serum IgA

   (b) *Secondary bacterial peritonitis*—is due to infection with aerobic and anaerobic bacteria and multiple organisms can be cultured from ascitic fluid.
   (c) *Tuberculous peritonitis.*
6. ***Hypersplenism.***
7. ***Chronic kidney failure***—An end-stage complication.

DIFFERENTIAL DIAGNOSIS

1. ***Depending upon clinical presentation of:***
   - Hepatomegaly
   - Haematemesis
   - Splenomegaly
   - Jaundice
   - Ascites
   - Encephalopathy
2. ***Two main types of cirrhosis***
   Table 32 depicts differentiating features between postnecrotic and alcoholic cirrhosis of liver.
3. ***Other rare types of cirrhosis***
   (a) Primary biliary cirrhosis

Table 33: Differentiating features between postnecrotic and biliary cirrhosis of liver

	Postnecrotic cirrhosis	*Biliary cirrhosis*
Incidence	Common	Rare
Age	40–60	Any
Sex	Male	Female
Malnutrition	Frequent	Rare
Jaundice	Uncommon, mild	Always present, marked
Liver	May be small	Always markedly enlarged
Spleen	Enlarged	Slight enlargement
Ascites	Frequent	Rare and late
Xanthomas	Absent	May be seen
Alkaline phosphatase	Not raised	Raised
Serum cholesterol	Normal or diminished	Elevated
Mitochondrial antibodies	Absent	Antimitochondrial antibody (AMA) present
Autoimmune disorders	Nil	Present (RA, diabetes, thyroid disturbances, Sjögren's syndrome)

Table 33 depicts differentiating features between postnecrotic and biliary cirrhosis of liver.

(b) Hemochromatosis:

Bronze skin pigmentation

Liver failure

Maturity onset diabetes mellitus

Arthropathy (chondrocalcinosis)

Cardiac failure

Loss of libido, testicular atrophy, infertility

Transferrin saturation > 62%

High serum ferritin levels usual

(c) Wilson's disease– Cirrhosis with associated signs of:

- CNS manifestations: Dementia, dysarthria, involuntary movements.
- Kayser-Fleischer ring.
- Renal tubular dysfunction –Aminoaciduria and possibly glycosuria.

4. ***Budd-Chiari syndrome***—This disorder is produced by obstruction of the venous drainage of the liver at any level from small hepatic veins to junction of IVC. The syndrome comprises triad of abdominal pain, ascites and hepatomegaly.

Aetiology: It can be due to lesions of large hepatic veins or to the central hepatic veins of individual lobules.

1. Obstruction of large hepatic veins—(a) Thrombosis e.g. in polycythaemia and prothorombotic conditions like factor V Leiden mutation, protein C and S deficiency, postpartum state rarely, after trauma and subphrenic abscess. (b) Neoplastic invasion particularly by a hypernephroma, and sometimes as part of thrombophlebitis complicating distant neoplasia.
2. Obstruction of small lobular veins due to toxins (veno-occlusive disease) and rarely drugs such as cytotoxic agents.
3. Presence of venous webs and valves.

Clinical Features:

1. *Fulminant form* presents with fulminant hepatic failure due to liver necrosis.
2. *Acute form* follows sudden venous occlusion (renal carcinoma, hepatoma, polycythaemia) with acute abdominal pain, vomiting, tender hepatomegaly, ascites and mild jaundice. If venous occlusion is total – delirium, hepatocellular failure and coma develop.
3. *Chronic form* more usual presentation. (a) Pain in abdomen, tender hepatomegaly and ascites. (b) Gradual development of portal hypertension and splenomegaly. (c) If IV obstruction—oedema feet, distended veins over abdomen flanks and back.

Diagnosis—(a) LFTs—Raised alkaline phosphatase and transaminases. (b) Ultrasound—Enlargement of caudal lobe, intra hepatic collaterals, echogenic areas due to occlusion of hepatic veins and ascites. (c) Doppler ultrasonography can detect abnormality of venous flow sufficient to establish the diagnosis. (d) Hepatovenography to detect extent of block and caval pressures.

Treatment—Anticoagulation is required and treatment of underlying pathology.

5. ***Non-cirrhotic portal fibrosis (NCPF)***—It is intrahepatic cause of portal hypertension with absence of hepatocellular damage and lack of nodular regeneration unlike cirrhosis. Possible etiological factors are – (a) Idiopathic portal hypertension. (b) Schistosomiasis. (c) Congenital hepatic fibrosis. (d) Chronic arsenic ingestion (from intake of deep tube-well water).

MANAGEMENT

Management is palliative.

I. Rest in bed to maximise treatment of any reversible element of underlying liver disease and to improve renal perfusion.

II. Correction of any etiological factor, e.g. abstinence from alcohol, prednisolone for chronic hepatitis, penicillamine for Wilson's disease, venesection and desferrioxamine for haemochromatosis, antiviral agents for viral hepatitis.

III. Diet—Low salt. Total daily intake of 2000 calories with protein intake of 120 gm. if patient can tolerate it. Fats and carbohydrates in normal amounts. Vitamin B complex.

IV. Drugs—(a) *Corticosteroids* – may help patient with active post-hepatitis cirrhosis. Prednisolone is continued in a small maintenance dose of 10 mg daily for many months. (b) *Immunosuppressive agents* – In case of troublesome side effects of corticosteroids. Azathioprine often of benefit in hepatitis, dose 50–75 mg daily.

V. Symptomatic treatment:

(a) ***Anaemia***—(a) Iron deficiency anaemia – Oral iron preparations or blood transfusion. (b) Macrocytic anaemia – Vitamin B_{12} and folic acid. (c) In some patients haemodilution is the main cause since the red cell mass is normal or slightly increased. Here splenectomy is recommended since it results in decrease in plasma volume and consequent increase in haemoglobin concentration.

(b) ***Restlessness—***All sedative drugs are potentially harmful but if patient becomes restless or noisy – Oxazepam or lorazepam

(c) **Ascites:**

1. *Low sodium diet*—Sodium intake up to 500 mg daily. No salt in cooking. Milk restricted to 4 oz and dairy products minimum. Sodium-free protein preparations can be given. Patients with hepatic ascites often have secondary hyperaldosteronism and a potassium chloride supplement may be required. Not more than1 litre fluid per day.

2. *Diuretics*:

First 4 days—Bed rest. Weigh patient and measure urine output daily, plasma urea, electrolytes and creatinine on alternate days. Give Pot. chloride 100 mEq daily.

After 4 days—If weight loss > 1 kg in presence of oedema or > 0.5 kg in absence of oedema, give Spironolactone 100–200 mg/day. Reduce dose of Pot. chloride by half.

After one week—If weight loss < 1 kg in 3 days, increase dose of Spironolactone by 100 mg. If painful gynecomastia is a side effect substitute Amiloride 10 mg b.d. If still no response, add Frusemide 40 mg and increase by 20 mg increments upto maximum of 120 mg.

Note: Over-diuresis may result in dehydration, uraemia and hyponatraemia and may precipitate hepatic encephalopathy. Stop diuretic if pre-coma (flap), hyponatraemia or alkalosis, or weight loss > 0.5 kg/day. Do therapeutic paracentesis and give albumin infusion if necessary. (Refer).

REFRACTORY ASCITES

Criteria for Diagnosis:

- No diuretic response despite spironolactone 400 mg/day, and frusemide 120 mg/day.
- Electrolyte changes or hypovolaemia limiting use of effective dose of diuretic.
- Repeated and frequent paracentesis.
- Non-compliance drug therapy and low salt diet.
- Hypokalaemia and alkalosis which impair renal tubular sodium excretion.

Factors which may precipitate development of refractory ascites:

- Deterioration of liver function due to liver cell damage or development of primary carcinoma or internal malignancy.
- SBP
- Chylous ascites
- Hepatic vein thrombosis

Management – Refer Ascites

9. ASCITES

CAUSES

Causes of ascites are listed in Table 34.

HISTORY

Personal history – Dietary habits and alcohol intake. Menstrual history in females.

Past history of tuberculosis or jaundice. History of haematemesis or piles.

Symptoms – Gain in weight, increase in girth of abdomen, abdominal discomfort and dyspnoea on exertion.

Table 34: Causes of ascites

1. **Disease of peritoneum**

Infections:
- Tuberculous peritonitis.
- Spontaneous bacterial peritonitis.
- Fungal – Candida, histoplasma.
- Parasitic – Schistosoma, enterobius.
- Viral – Acute severe hepatitis.

Neoplasms:
- Primary mesothelioma.
- Secondary carcinomatosis, e.g. adenocarcinoma, sarcoma, teratoma, leukaemia, Hodgkin's disease, lymphocytic lymphoma, myeloid metaplasia.

Pseudomyxoma peritonei

Familial paroxysmal peritonitis

Miscellaneous
- Vasculitis – SLE and other collagen vascular diseases, allergic vasculitis (Henoch-Schonlein purpura).
- Eosinophilic gastroenteritis.
- Whipple's disease.
- Granulomatous peritonitis – Sarcoidosis, Crohn's disease, starch peritonitis.
- Peritoneal loose bodies.
- Peritoneal encapsulation.

2. **Portal hypertension**
3. **Congestive heart failure**
4. **Hypoalbuminemia**
   - Nephrosis
   - Malnutrition
   - Protein-losing enteropathy
5. **Beriberi**
6. **Myxoedema**
7. **Ovarian disease:**
   - Meigs' syndrome
   - Struma ovari
   - Ovarian overstimulation syndrome
8. **Pancreatic ascites** due to retroperitoneal leakage of pancreatic enzymes from a ruptured cyst or pancreatic duct.
9. **Bile ascites**
10. **Chylous ascites**
11. **Epidemic dropsy**

Mode of onset in relation to oedema of lower extremities or elsewhere. In cirrhosis the oedema always follows the ascites in contraindication to other forms of oedema which precede the ascites.

PHYSICAL EXAMINATION

(a) Signs

1. *General appearance*—'Spider man'—thin limbs with protuberant abdomen.

Table 35: Ascites in absence of peripheral oedema

- Cirrhosis
- Tuberculous peritonitis
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Hepatic venous occlusion
- Intra-abdominal tumour

2. *Of free fluid in peritoneal cavity*—Generalised abdominal distension, bulging in the flanks, umbilicus transversely stretched or everted, central tympany and shifting dullness, fluid thrill.
3. *Of increased intra-abdominal pressure*—Abdominal wall hernias (umbilical or inguinal), divarication of recti, increased inferior vena cava pressure causing lower limb oedema (Table 35) and abdominal wall venous collaterals.
4. *Of causative condition*—e.g. (a) Portal hypertension—Splenomegaly, portal-systemic venous collaterals. (b) Chronic liver disease—Peripheral stigmas of chronic liver disease, or cholestasis, hepatic encephalopathy. (c) Evidence of tuberculosis elsewhere in tuberculous peritonitis.
5. *Rectal examination* for hemorrhoids, malignant lesion in pelvis or fluid in pouch of Douglas.

SPECIAL INVESTIGATIONS

Ascitic Fluid Analysis

Macroscopic Appearance

- *Clear*—usually occurs in congestive heart failure, hypoalbuminemia, cirrhosis, inferior vena cava obstruction, Budd-Chiari syndrome, Meigs' syndrome and vasculitis.
- *Turbid* is common in tuberculous peritonitis, peritoneal malignancy, bacterial peritonitis, pancreatic ascites, and myxoedema.
- *Haemorrhagic*—Traumatic tap, tuberculosis, acute haemorrhagic pancreatitis, mesenteric artery thrombosis, malignancy involving peritoneum or liver surface, benign hepatic adenoma or spontaneous bleeding from intra-abdominal portal-systemic collaterals.
- *Chylous (milky)*—Trauma to thoracic duct, filariasis, congenital. Tuberculosis, malignancy involving lymphatic system, or spontaneous; cirrhosis, nephrotic syndrome, protein-losing enteropathy, surgical or traumatic rupture of lymphatics which is not uncommon

Table 36: SAAG and causes of ascites

High gradient (>1.1 g/dL)		*Low gradient (<1.1 g/dL)*
Ascitic protein <2.5 gm/dL	Ascitic protein >2.5 gm/dL	
Cirrhosis Late Budd-Chiari syndrome Massive liver metastasis	Alcoholic hepatitis Cardiac ascites Early Budd-Chiari syndrome Portal vein thrombosis Veno-occlusive disease	Peritoneal carcinomatosis Tuberculous peritonitis Pancreatic ascites Biliary ascites Nephrotic syndrome Serositis of collagen vascular disease

after distal splenorenal shunt surgery. Lymphoma and other malignancies. Ether extraction of the fluid will lead to clearance of the turbidity.

- *Pseudochylous*—Turbid fluid due to leucocytes or tumour cells. Alkalinization of fluid will reduce turbidity.
- *Mucinous*—Pseudomyxoma peritonei or rarely colloid carcinoma of stomach or colon with peritoneal implants.

Cytology

- *Red cells*—If fluid is haemorrhagic.
- *White cells*—Polymorphs in peritoneal irritation caused by inflammation, infection or tumour. Lymphocytes and monocytes in tuberculosis. More than 250 neutrophils/mm^3 suggestive of SBP. Eosinophils in enteritis and peritonitis.
- *Malignant cells*—in carcinomatosis.

Biochemistry

- *Protein content* seldom exceeds 1.5 g/dL. Higher values indicate infection, hepatic venous obstruction or malignancy. Low values (< 1.0 g/dL) indicate high risk of developing SBP.
- *Serum-ascites albumin gradient*

SAAG is more useful than total protein concentration of ascitic fluid (Table 36). The gradient is physiologically based on oncotic hydrostatic balance and is related directly to portal pressure. SAAG = Albumin (serum) – Albumin (ascites). Patients with gradients >1.1 gm/dL have portal hypertension, patients with gradient <1.1 gm/dL do not.

- *Glucose*—Glucose concentration is normal if fluid is not infected as in spontaneous bacterial peritonitis, but is usually < 3.0 mmol/L in secondary bacterial peritonitis. Values less than 60 mg/100 mL may suggest neoplastic effusion.

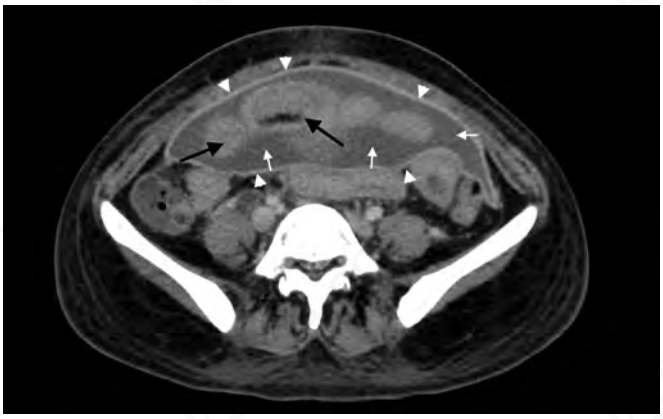


Fig. 8: CECT abdomen in bacterial peritonitis showing thickened enhancing peritoneum (arrow heads), ascites (thin white arrow) and intestines in fluid (thick black arrow)

- *Ascitic amylase* high in pancreatic ascites.
- *Triglycerides* elevated in chylous ascites.
- *Additional tests:*

(i) Adenosine deaminase if tuberculosis is suspected. (ii) pH, lactate dehydrogenase if bacterial peritonitis is suspected. (iii) High levels of interleukin-6 and tumour necrosis factor in cirrhotic ascites. (iv) High levels of cytokines in aspirate fluid of patients with SBP and related complications such as impaired circulatory and renal function. (v) Serum CA-125 and ascitic fluid cytology.

Additional Tests

1. SBP in patient with cirrhosis and ascites has high mortality. Positive bacterial culture of ascitic fluid is necessary for confirming diagnosis.
2. Investigations for suspected portal venous hypertension (*see* portal hypertension).
3. Ultrasonography can detect as little as 100 mL of abdominal fluid and may suggest the cause.
4. Liver biopsy of value in cirrhosis or malignancy of liver.
5. Liver function tests to confirm cirrhosis.
6. Liver scan for space occupying lesions of the liver.
7. Laparoscopy—Useful for (i) paracentesis, (ii) direct visualization of abdominal viscera, (iii) biopsy of liver.
8. Selective arteriography of the hepatic and splenic arteries with delayed films to visualise the portal vein may be helpful in ascites of obscure cause.
9. Needle Biopsy of peritoneum for diagnosis of tuberculous and malignant peritonitis.
10. CT scan (Fig. 8).
11. Laparotomy may be required in some cases.

Table 37: Ascitic fluid characteristics according to etiology

Aetiology	*Protein (g/dL)*	*WBCs/mm³*	*RBCs/mm³*	*Other*
Cirrhosis / portal hypertension	<2.5	300–500 (70% mononuclear)	Usually <1000	Serum-ascites albumin gradient >1.1 g/dL
Hepatocellular carcinoma	<2.5	300–500 (70% mononuclear)	Usually 1000 but may be >50,000	Cytology for neoplastic cells negative
Peritoneal carcinomatosis	>2.5	Variable (Mononuclear predom.)	Usually <1000 but may be >50,000	Neoplastic cells on cytology
Cardiogenic ascites	>2.5-3	300–500 (Mononuclear predom.)	<1000	Serum-ascites albumin gradient <1.1 g/dL
Pancreatic ascites	> 2.5	300–500 (Mononuclear predom.)	<1000	Very high amylase and lipase
TB peritonitis	>3 (may be <2.5 in cirrhotics)	>500 (Mononuclear predom.)	<1000	Elevated adenosine deaminase and lactic dehydrogenase
Spontaneous bacterial peritonitis	<2.5	>250 neutrophils	<1000	Normal glucose, pH, Lactic dehydrogenase
Bacterial peritonitis	>2.5 usually	>1000 neutrophils	Variable	Low glucose and pH Lactic dehydrogenase and amylase Bacteria on Gram stain

DIFFERENTIAL DIAGNOSIS

I. **Differential diagnosis according to ascitic fluid characteristics**

Differential diagnosis according to ascitic fluid characteristics is given in Table 37.

II. **Other causes of abdominal distension** –

1. *Pregnancy*—History of amenorrhoea. Percussion dullness central with tympany in flanks. Little change in note on change of posture. Foetal parts may be palpable.
2. *Excessive fat*—Abdomen usually enlarged out of proportion to rest of body and pendulous. No shifting dullness or fluid thrill. Symmetrical globular enlargement with accentuation of cutaneous folds.
3. *Tumours*—Abdominal dullness limited to area overlying growth. In ovarian tumours, distance between xiphisternum and umbilicus less than distance between umbilicus and symphysis. Vaginal examination diagnostic. Menstrual disturbances.
4. *Gaseous distension*—Tympanitic note if colonic distension, most marked in periphery. Prominence of epigastrium if undue distension of stomach.
5. *Distended bladder*—An over-distended bladder may be felt as a somewhat tender and rounded cystic mass above the symphysis pubis and extending upwards even up to the umbilicus.
6. *Abdominal proptosis*—Distension produced by contraction of diaphragm and exaggerated lumbar lordosis which is obvious on clinical examination. It is a psychiatric complaint.

III. **Other causes of ascites:**

(a) ***Ascites only or with oedema of feet:***

1. *Cirrhosis of liver*
2. *Tuberculous peritonitis* (Table 38)
3. *Malignant ascites*—Symptoms and localising signs due to primary tumour. Liver may be enlarged and nodular.

   Peritoneal fluid may be haemorrhagic. High protein content, high serum-ascites albumin gradient (>1.1), high lactic acid dehydrogenase level, and high cholesterol values (>48 mg/dL). If necessary further confirmation by peritoneoscopy and peritoneal biopsy.
4. *Portal hypertension* (other than cirrhosis):
   (a) Obstruction to portal vein by enlarged glands—Presence of primary growth or enlarged lymph nodes elsewhere. Progressive jaundice.
   (b) Thrombosis of portal vein—Rapid development of ascites, hematemesis, melena and splenomegaly.
5. *Constrictive pericarditis:*
   - Presence of signs of congestive failure without signs of heart disease.

Table 38: Ascitic fluid in cirrhosis of liver vs TB peritonitis

	Cirrhosis of liver	*TB peritonitis*
Age	Usually middle age	Adolescent or young adults
Amount of fluid	Usually large	Small, moderate, or large
Liver	May not be palpable,	Not enlarged, if palpable firm and regular edge
Fever	Absent	Present
Tenderness of abdomen	Rare	Common
Other features	Emaciation, dyspepsia, evidences of collateral circulation, liver function impaired	Primary focus in the lungs may be found Lumps of matted omentum may be palpated
Ascitic fluid	Transudate	Exudate, predominantly lymphocytic
Laparotomy	Nodular liver surface	Peritoneum studded with small granulomas

- Impalpable apex beat.
- Rise of jugular venous pressure on inspiration.
- Hepatomegaly and ascites
- 3rd heart sound (Pericardial knock sound).
- Pulsus paradoxus.
- Calcification of pericardium.

6. *Budd-Chiari syndrome* – Onset of:
   (a) Hepatic vein obstruction indicated by – pain, hepatic enlargement, vomiting and ascites. Liver large and tender. Failure of jugular veins to fill when liver is pressed. Condition suspected in presence of disorders of coagulation or malignant disease.
   (b) Thrombosis of major venous channels such as portal vein will cause abdominal pain, ascites and bloody diarrhoea.
   (c) Blockage of inferior vena cava may lead to albuminuria, prominent veins in the loin and rarely nephrotic syndrome.

   Ascitic fluid—High protein content.

   Ultrasound—Hepatic vein abnormalities, caudate lobe hypertrophy and compression of IVC.
7. *Spontaneous bacterial peritonitis (SBP)* Should be considered in –
   - Patients with pre-existing ascites who develop fever or changing abdominal signs and symptoms.
   - Patient with a focus for bacteraemia such as indwelling catheters, cellulitis, or urinary, biliary or pulmonary infection.
   - Patients with decreased immunological competence, e.g. hypogammaglobulinemia.
   - Predictive indices for diagnosis include – Ascitic fluid polymorphonuclear count greater than 250/cm^3, ascitic fluid pH <7.3.
   - GI hemorrhage.
   - Ascitic fluid cloudy with protein <1 g/dL, especially those with high bilirubin >2 mg/dL or low platelet count <98,000 cells/mm^3).
   - Patients with hepatic encephalopathy.
   - May present as abrupt deterioration or hepatic encephalopathy in a patient with cirrhosis and ascites.
8. *Bacterial peritonitis* should be suspected when ascitic fluid analysis shows 2 or 3 of the following criteria: Total protein >1 gm/dL, glucose <50mg/dL, and LDH >225 IU/mL. Most of the ascitic fluid cultures in such cases are polymicrobial, whereas in SBP the infection is usually monomicrobial (commonly *E. coli*).
9. *Chylous ascites*—Due to obstruction of receptaculum chyli and thoracic duct by filariasis, neoplasms (intra-abdominal or thoracic), inflammations (mesenteric adenitis, tuberculosis, pancreatitis), traumatic rupture of thoracic duct, or idiopathic. Turbid fluid which separates into layers and contains lymphocytes.
10. *Pancreatic ascites*—Intermittent abdominal pain with rarely gross refractory ascites. Serum amylase elevated.
11. *Meigs' syndrome*—Triad of ascites, hydrothorax and fibroma of the ovary. The hydrothorax and ascites disappear when the ovarian tumour is removed.
12. *Pseudomyxoma peritonei*—Due to rupture of mucocoele of appendix or pseudomucinous cyst of ovary. Increasing abdominal girth, and occasional attacks of abdominal pain. Abdominal masses may be palpable; there is often a fluid thrill and sometimes shifting dullness. Disparity between amount of ascites and clinical state of patient. On paracentesis mucinous material often too sticky to be aspirated.

Table 39: Ascites in congestive heart failure vs nephrosis

Congestive heart failure	*Nephrosis*
Starts in feet	Starts as puffiness of face
Oedema maximum in evening	Oedema maximum in morning
Cyanosis	Pallor
Raised JVP	JVP normal
Heart always enlarged	Cardiac enlargement rare
Liver enlarged and tender	Liver not palpable.
	Oedema of abdominal wall common
Trace proteinuria	Massive proteinuria

13. *Bile ascites*—Extravasated bile may cause chronic peritoneal fluid accumulation. Abdominal distension after biliary tract surgery. Nausea, malaise, jaundice and acholic stools. Paracentesis yields bilious fluid.
14. *Hypothyroidism*—Impaired mentation often without other features of the disease. Yellow gelatinous fluid with proteins generally more than 4 gm per 100 mL. Ascites clears within 2–3 weeks after starting thyroxine.

b. ***Ascites with generalized anasarca:***

1. *Congestive heart failure*
2. *Nephrosis* (Table 39)
3. *Anaemia and hypoproteinaemia:*
   - Gross anaemia.
   - Marked oedema of feet.
   - Ascites slight or moderate.
   - Spleen may be enlarged.
   - Serum proteins diminished, reversal of albumin globulin ratio.
4. *Beriberi:*
   - Symptoms of cardiac involvement.
   - Heart enlarged
   - Tachycardia
   - Tenderness of calf muscles and blunting of sensation.
   - Oedema firmer than that of nephrosis and does not involve scrotum.
   - Absent or sluggish deep reflexes.
   - Decreased urinary output of thiamine.
5. *Epidemic dropsy:*
   - Oedema of legs occurring in several members of the family, or several individuals in same locality.
   - Marked tenderness over oedematous parts in most cases and severe burning of feet with paraesthesiae in majority.
   - Preceding or accompanying gastro-intestinal symptoms.
   - Diffuse blotchy erythema of skin
   - Presence of cardiovascular symptoms.
   - Glaucoma.
   - Cutaneous nodules.
   - Detection of argemone oil in cooking medium.

Table 40: Indications for therapeutic paracentesis

- Marked abdominal discomfort.
- Cardiac or respiratory embarrassment (Tense ascites).
- Oliguria.
- Anorexia and dyspepsia.
- Following haematemesis in cirrhosis to reduce congestion.
- Patients refractory to full medical therapy.
- Danger of strangulation of secondary herniae.

MANAGEMENT

Of the cause—Digitalis for cardiac failure, anti-tuberculous drugs for tuberculous peritonitis, pericardiolysis for constrictive pericarditis, Vitamin B_1 for beriberi.

Of ascites itself:

1. Bed rest improves renal perfusion.
2. Diet—Low sodium diet if fluid non-inflammatory. Restrict fluid to 1 litre/day.
3. Diuretics—Spironolactone 100 mg, if no response, add frusemide 40 mg. Increase doses stepwise to spironolactone 400 mg and frusemide 160 mg. Aim is to achieve weight loss of 300–500 g/day in ascitic patients with peripheral oedema.
4. Therapeutic paracentesis (Table 40)

   Technique: Ask patient to empty his bladder and prop him up in bed. Paracentesis is usually performed in the right iliac fossa, avoiding inferior epigastric vessels, visible venous collaterals and scars of previous operations. The skin is cleansed and local anaesthetic infiltrated through to the peritoneum. To minimise chances of subsequent leakage of ascitic fluid, a thin bore needle (21–23 gauge) attached to a 20 mL syringe is used. The aspiration needle is inserted through the skin, which is then pulled sideways and the needle pushed through the abdominal wall, muscle and peritoneum. The fluid is drained slowly.

An abdominal binder or many-tailed bandage is placed round the abdomen and it is tightened as required. Paracentesis can also be performed with special needle with side holes, attached to low grade suction.

Complications and Management:

(a) *Fainting*—Due to too rapid removal of fluid. Further removal should be stopped. If recovery is slow administer 500 mL 5% glucose IV. If marked fall in B.P. 200 mL 5% saline by infusion.

(b) *Infection*—Acute peritonitis very rare but chronic infection may result from repeated paracentesis. If organism is cultured from sample of fluid give appropriate antibiotics.

(c) *Perforation of viscus*—Rare. Usually gives rise to localised peritonitis treated with gentamicin and broad spectrum antibiotics.

(d) *Acute liver failure.*

(e) *Depletion of proteins*—Removal of 5 litres of ascitic fluid may involve loss of 50–100 gm. protein; can be avoided by giving simultaneous albumin infusion.

A total paracentesis can be carried out with concomitant infusion of 6–8 g of salt-poor albumin for every litre of ascitic fluid drained. 8 gm/litre of ascitic fluid removed to prevent post-paracentesis circulatory dysfunction (PICD) which is associated with increased risk of recurrence of ascites, greater diuretic requirements and shorter survival. No differences have been observed between albumin and other plasma expanders when < 5 litres are removed. Contraindicated in patients with grade C hepatic dysfunction, serum bilirubin > 10 gm/dL, prothrombin time < 40%, platelets < 40000, creatine or urine sodium < 10 mEq/24 hours.

5. Peritoneovenous shunt is as effective as paracentesis in control of refractory ascites but is reserved for patients who are not candidates for liver transplantation, TIPS placement or repeated large volume paracentesis.
6. TIPS is the only treatment aimed at relieving portal pressure and should be used in patients who respond poorly to paracentesis (compartmentalization of ascitic fluid, and those who need repeated taps often). In patients of cirrhosis, TIPS is associated with increased frequency of hepatic encephalopathy.

REFRACTORY (INTRACTABLE) ASCITES

Common causes: Portal hypertension, CHF, chronic kidney failure, tuberculosis and malignancies.

Tr. of refractory ascites in cirrhosis—(a) Removal of large amount of fluid (3–5 L) over 1–2 hours. Salt-free albumin 8 g/litre of ascitic fluid removed or Dextran. (b) LeVeen shunt if infection, IVC thrombosis, pulmonary oedema, bleeding from oesophageal varices, DIC. (c) Side-to-side portocaval shunt. (d) Liver transplantation.

Table 41: Causes of generalized portal hypertension

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Extra-hepatic portal vein obstruction (Fig. 9)
Massive splenomegaly (Banti's syndrome)
Intrahepatic
Cirrhosis
Schistosomiasis
Idiopathic noncirrhotic portal hypertension
Congenital hepatic fibrosis
Granulomata
Metastatic malignant disease
Posthepatic
Budd-Chiari syndrome
Veno-occlusive disease
Constrictive pericarditis
Congestive heart failure
Inferior vena cava webs

10. PORTAL HYPERTENSION

CAUSES

Causes of generalized portal hypertension, according to site of portal venous obstruction (Table 41 and Fig. 10).

MEASUREMENT OF PORTAL VENOUS PRESSURE

Wedged hepatic venous pressure (WHVP)—A cardiac catheter is passed to a hepatic vein under radiographic control until it 'wedges' in a hepatic venule and the pressure measured at that point. Normal 5–6 mm Hg.

Transhepatic—A 25-guage needle is used under ultrasound guidance, the needle being replaced by catheter which is placed in the main portal vein.

COLLATERAL CIRCULATION

Abnormal communications (collateral channels, portosystemic anastomosis) develop between the portal vein and systemic veins. There are 4 main groups as given in Table 42.

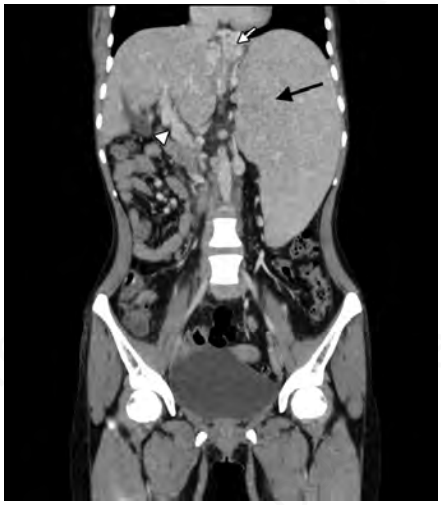


Fig. 9: CECT abdomen venous phase showing extra-hepatic portal venous obstruction (EHPVO) with splenomegaly (black arrow), oesophageal varices (white arrow) and portal cavernoma (arrowhead)

Table 42: Portosystemic anastomosis

Site	*Portal vessel*	*Caval vessel*
I. Cardio-oesophageal Junction (Figs. 11 and 12)	Left gastric, posterior gastric, short gastric	Intercostal Diaphragmo-oesophageal Azygos minor
Lower end of rectum (Haemorrhoids)	Superior haemorrhoidal	Inferior haemorrhoidal + middle haemorrhoidal veins
II. Periumbilical or abdominal wall	Vein in falciform ligament	Para-umbilical veins
III. Site of contact of abdominal organs with retroperitoneal tissues	Hepatic vein Vein in ileorenal ligament	Diaphragmatic vein Omental vein Lumbar vein
IV. Retroperitoneal space	Portal vein	Left renal vein through blood entering directly from splenic vein via diaphragmatic, spermatic, left adrenal or gastric veins.

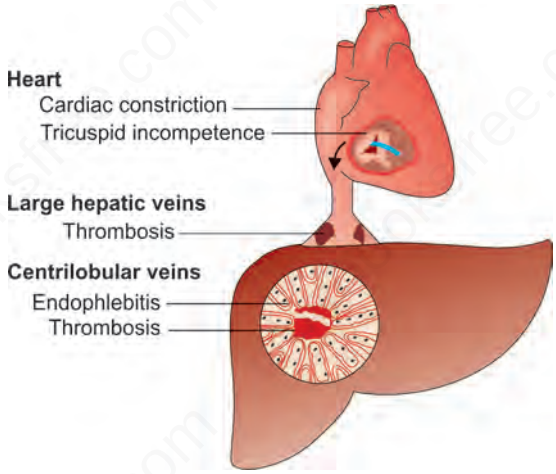


Fig. 10: Causes of increased venous pressure

HISTORY

Cirrhosis is the commonest cause hence relevant to it – hepatitis, alcohol. Hematemesis is the commonest presentation; melena without hematemesis may result from bleeding varices. Clotting disease and some drugs, e.g. oral contraceptives predispose to portal and hepatic venous thrombosis.

EXAMINATION

Abdominal wall veins are often prominent and rarely, they may form a caput medusae around the umbilicus.

Murmurs—A venous hum may be heard over the collaterals radiating occasionally to the precordium or over liver (Cruveilhier-Baumgarten syndrome). A thrill may be felt at the site of maximum intensity. An arterial systolic murmur suggests primary liver cancer or alcoholic hepatitis. The paraxiphoid umbilical veins indicate intrahepatic portal venous hypertension.

Spleen—Enlarges progressively, the edge is firm. Massive if presinusoidal portal obstruction, cirrhosis with hypersplenism, rarely tropical splenomegaly.

Liver—High pressures are more often associated with a small, fibrotic liver. A soft liver suggests extrahepatic portal venous obstruction, a firm liver cirrhosis.

Ascites—Portal hypertension raises capillary filtration pressure and increases quantity of ascitic fluid.

INVESTIGATIONS

Ultrasonography and Echo-Doppler ultrasonography should exclude an obvious space-occupying lesion and establish patency of the portal and hepatic veins.

Retrograde CO_2 portography – or splanchnic arteriography may be necessary to visualize the portal vein.

Portal venography demonstrates the site and often the cause of portal venous obstruction and is performed prior to surgery. A typical 'spider web' appearance on hepatic venography is diagnostic of Budd-Chiari syndrome.

Portal venous pressure measurements are seldom needed but can be used to confirm portal hypertension and differentiate sinusoidal from presinusoidal lesions.

Note: Minimal use or avoidance of radiological contrast (e.g. angiography) to minimize renal dysfunction.

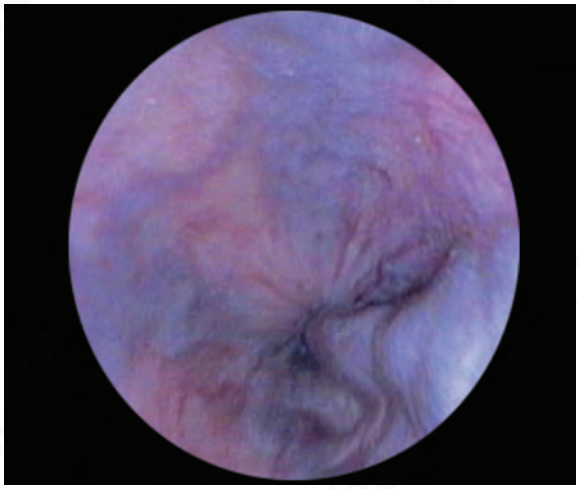


Fig. 11: OGD scopy showing oesophageal varices

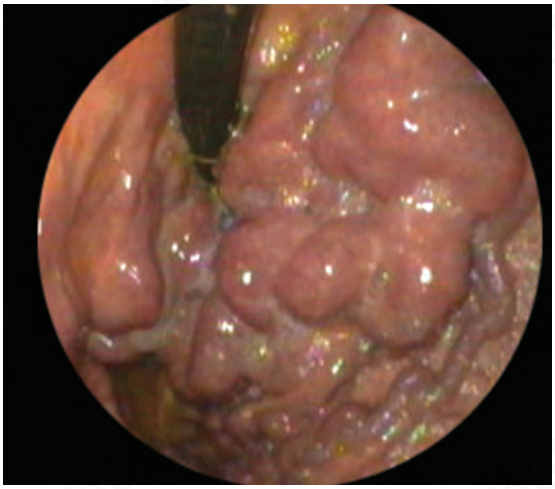


Fig. 12: OGD scopy showing gastric varices

COMPLICATIONS

Complications of portal hypertension are listed in Table 43.

MANAGEMENT

Major venous hepatic obstruction—(a) Thrombolytic therapy if seen soon after onset. (b) Side-to-side shunt between portal vein and IVC relieves hepatic engorgement and thus improves liver function. (c) Hepatic transplantation.

Variceal bleeding (Refer).

Table 43: Complications of portal hypertension

• Variceal bleeding: In cirrhotics risk of bleeding is related to:
Size of varices
Presence of red signs at endoscopy (red weal marks)
Degree of liver dysfunction
• Ascites
• Congestive gastropathy
• Hypersplenism
• Hepatic encephalopathy
• Kidney failure

11. HEPATOMEGALY

CAUSES

Causes of hepatomegaly are enumerated in Table 44.

DIFFERENTIAL DIAGNOSIS OF HEPATOMEGALY

1. Hepatitis:
   (a) *Viral hepatitis*—Prodromal symptoms of gastrointestinal upset, abdominal discomfort, anorexia, malaise and fever followed by dark urine and jaundice. Enlarged tender liver with smooth edge. Spleen palpable.
   (b) *Amoebic abscess*—Moderate to huge enlargement of liver, pain in hepatic region and liver or intercostal tenderness. Moderate pyrexia, at times fever with rigors. Caecal tenderness may be found and history of diarrhoea with mucus and blood may be obtained. Spleen not palpable. Moderate leucocytosis. Diagnostic aspiration may show anchovy sauce pus if abscess and ultrasonography hypoechoic area with ragged edges.
   (c) *Acute alcoholic hepatitis*—Commonly follows a period of heavy drinking. Right u©pper abdominal pain, anorexia, nausea and vomiting, and profound weakness. Jaundice common. Fever may occur. Liver usually enlarged and tender. Spider naevi may develop. Arterial bruit may be heard over the liver. Ascites develops rapidly.
   (d) *Autoimmune hepatitis*—High preponderance in young females. Clinical features – (i) Hepatic – Jaundice, spider naevi, enlarged spleen. (ii) Nonspecific – Pyrexia, malaise, lethargy, etc. (iii) Multisystem features – Rashes, arthritis, pleurisy, pericarditis, myocarditis, nephritis, etc. (iv) Liver biopsy is the most important diagnostic test. (v) Non-organ-specific autoantibodies are important in establishing the diagnosis.

Table 44: Causes of hepatomegaly
Infections
Viral – Viral hepatitis, yellow fever, infectious mononucleosis, Lassa fever
Bacterial – Typhoid, pneumonia, brucellosis, tuberculosis
Protozoal – Amoebiasis, malaria, kala azar
Spirochaetal – Weil's disease, syphilis, relapsing fever
Parasitic – Schistosomiasis, echinococcus, clonorchiasis
Fungal – Actinomycosis, histoplasmosis
Metabolic
Fatty liver
Amyloid
Glycogen storage disease
Congestive
(a) *General* – Congestive heart failure, tricuspid regurgitation, constrictive pericarditis
(b) *Local* – Portal hypertension (cirrhosis), hepatic vein thrombosis
Tumours
Primary: Benign and malignant hepatoma, benign and malignant cholangioma, fibroma, sarcoma, haemangioma
Secondary – Direct due to spread by contiguity, or embolic metastatic
Cysts
Hydatid
Polycystic
Biliary obstruction – Gallstones, strictures of bile ducts
Haematological
Leukaemias
Lymphoma
Myeloproliferative disorders
Storage disorders – Gaucher's disease, Niemann-Pick's disease, amyloidosis, glycogen storage disease, gargoylism, haemochromatosis
Myeloid metaplasia – Secondary carcinoma of bone, myelofibrosis, myelosclerosis, multiple myeloma, marble-bone disease
Genetic abnormalities – Sickle cell disease
Congenital – Riedel's lobe

2. Portal cirrhosis—(i) Evidence of hepatocellular damage – Dyspeptic symptoms, vascular spiders, alopecia, palmar erythema. Palpable liver in about 75% of patients (ii) Evidence of portal hypertension – Palpable spleen, ascites in later stages, oesophageal varices, hemorrhoids.
3. Congestive heart failure—Slight to huge enlargement of liver. Edge firm, smooth and tender on palpation. Spleen may be palpable. Ascites in severe cases. Increased venous pressure and other signs of congestive failure. Pulsatile liver if tricuspid regurgitation.
4. Malignant hepatic tumours:
   (a) *Hepatocellular carcinoma*—Male predominance. About 80% in cirrhotic livers. In addition 80% are associated with markers of prior HBV infection, and also HCV.

   Symptoms—Vague right upper quadrant pain, nausea, vomiting, jaundice. Signs –Hepatomegaly (nodularity, hard and may be tender) jaundice, ascites, cachexia, fever.

   Diagnosis—Abnormal LFTs, and raised α-fetoprotein.

   Imaging—Ultrasonography and biphasic contrast enhanced CT detect lesions as small as 5 mm. CT following injection of iodised oil emulsion into hepatic artery can detect lesions that appear equivocal on plain scan (Fig. 13).

   (b) *Uncommon tumors* include angiosarcomas, haemangioendotheliomas and mesenchymal tumors. Diagnosis is based on clinically palpable liver and ultrasonography or CT.

   (c) *Metastatic tumors*—Liver is the most common site of metastatic disease after the lymph nodes. (a) Colorectal cancer. About 50% develop hepatic metastasis. Diagnosis on scanning. (b) Neuroendocrine tumors of pancreatic origin and carcinoid often metastasize to the liver.
5. Malaria—Liver may be palpable in about half the cases. Spleen always palpable. Jaundice rare, transient. Fever with rigors. Demonstration of malarial parasites, and therapeutic response to antimalarial drugs.
6. Alcoholic fatty liver—Liver enlarged, smooth, firm, non-tender. No enlargement of spleen. One may sometimes find hemolytic anaemia, jaundice and turbid serum due to hyperlipidaemia or marked cholestasis suggesting extrahepatic obstruction.
7. Kalaazar—Some degree of liver enlargement always present. Progressive enlargement of spleen, long continued fever, loss of weight, anaemia, bleeding tendencies and increasing darkness of complexion. Demonstration of Leishman-Donovan bodies in sternal smear.
8. Leukaemia—Smooth enlargement of liver, moderate in myeloid, gross in lymphoid leukaemia, massive splenomegaly, anaemia. Blood picture or at times needle biopsy of liver confirms diagnosis.

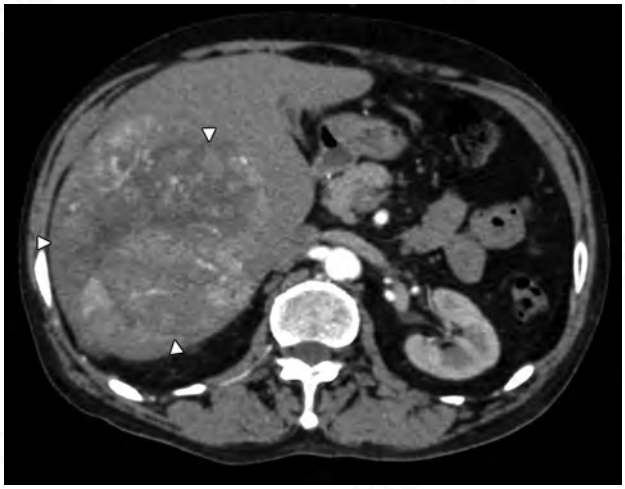


Fig. 13: CECT abdomen arterial phase showing enhancing large hepatocellular carcinoma (arrow heads)

9. Hodgkin's disease—Hepatosplenomegaly develops during course of the disease. Rubbery, non-tender lymph nodes usually in neck. Systemic symptoms like weight loss, night sweats, fever or pruritus. Raised ESR. Gland (or liver) biopsy reveals Sternberg-Reed binucleate giant cells.
10. PYOGENIC liver abscess or abscesses—Pain and tenderness localised in hepatic area, chills and fever. High leucocyte count. Location and number of abscess(es) determined by CT scan, sonography. Positive blood culture of pus or tissue aspirated from liver helpful in diagnosis and treatment.
11. Miliary tuberculosis—Tender liver edge. Pyrexia. Concomitant active tuberculosis elsewhere and other features of haematogenous dissemination.
12. Primary biliary cirrhosis (PBC)—Predominantly in females. Hepatomegaly and pruritus with or without jaundice. There may be pigmentation, xanthelasma, splenomegaly, ascites and bleeding varices. Elevated serum ALP and α-glutamyl transferase present in 95%.
13. Tropical splenomegaly syndrome (TSS)—Gross splenomegaly with moderate hepatomegaly in immune adults from areas of endemic malaria. Raised malarial antibody titres, high serum IgM level. Liver biopsy – Hepatic sinusoidal lymphocytosis. Absence of malarial parasites on peripheral smear.
14. Budd-chiari syndrome—(Hepatic venous obstruction) – Liver enlarged and tender. Failure of jugular veins to fill when liver is pressed. Ascites. Ascitic fluid of high protein content and may be blood stained.
15. Sickle cell disease—Moderate enlargement of liver with jaundice. Sickled red cells.
16. Hydatid cyst—Firm, smooth, non-tender liver. No jaundice, no splenic enlargement. History of contact with dogs. At times pyrexia of unknown origin following secondary pyogenic infection. Jaundice may occur due to pressure on bile ducts. Hydatid thrill may be elicited. Eosinophilia. Plain radiograph of abdomen – calcification in long-standing liver hydatids. Ultrasound – Cysts with characteristic appearances of daughter cysts and scolices inside them.
17. Hemochromatosis—Hepatomegaly with predisposition to cirrhosis. Lethargy. Arthralgia with swelling of second and third metacarpal joints in early stages, late chondrocalcinosis of large and small joints. Skin pigmentation limited to shins and light-exposed areas. Elevated serum iron content. Measurement of chelatable iron excretion in urine after injection of desferrioxamine 10 mg/ kg body wt. – more than 2 mg of ferrioxamine excreted in 24 hours. Diagnostic histology on liver biopsy.
18. *Syphilis of the liver*—Firm, irregular enlargement. Stigmata of syphilis and positive serology. Therapeutic test in doubtful cases with iodides and penicillin will produce reduction of swelling and of local tenderness.
19. *Schistosomiasis*—Hepatomegaly with portal hypertension, splenomegaly, oesophageal varices and dependent oedema. Liver failure may lead to gynecomastia, scanty body hair and stunted growth. Diagnosis is established by remnants of lateral spinal eggs of Schistosoma, pigments, granulomas and portal fibrosis on liver biopsy.
20. *Clonorchiasis*—Due to infestation with Clonorchis sinensis (liver fluke). Advanced disease is characterised by hepatomegaly, ascites and oedema. Malignant change may lead to carcinoma of bile ducts or liver. Eosinophilia and raised alkaline phosphatase. Diagnosis confirmed by demonstration of eggs in faeces or in bile obtained by duodenal intubation.
21. *Amyloidosis*—Liver usually large, smooth, rubbery and nontender. Jaundice and ascites may occur. Generalised oedema common. Albuminuria and evidence of chronic sepsis or rheumatoid arthritis. Liver function tests normal. Aspiration liver biopsy, or kidney biopsy or rectal biopsy shows amyloid material.
22. *Myeloid metaplasia*—It can occur in conditions of bone marrow replacement or irritation. Liver enlarged with firm smooth edge. Massive spleen. Jaundice rare.

Liver function tests normal. Primitive leucocytes or red cells in the peripheral blood.

23. *Gaucher's disease*—Hepatosplenomegaly, pigmentation of exposed parts. Wedge-shaped thickening of conjunctivae at angles of eyes. Spontaneous bone fractures or bone pain with fever. X-rays of long bones like femur show expansion of lower end. Sternal marrow will show large pale Gaucher cells with fibrillary cytoplasm and eccentric hyperchromatic nuclei.

12. LIVER DISEASE IN PREGNANCY

LIVER DISEASE SPECIFIC TO PREGNANCY

1. ***Liver dysfunction in hyperemesis gravidarum*** is generally mild and resolves as the vomiting settles. IV dextrose 5% is useful.
2. ***Cholestasis of pregnancy*** usually presents as pruritus of extremities in last trimester of pregnancy but can be earlier. Jaundice is uncommon, ALT elevation is the routine test; serum bile acid elevation confirms the diagnosis when routine LFTs are normal. It is more common in multiple gestations and in women given progesterone supplements during pregnancy.

   Treatment: Ursodeoxycholic acid, 10 mg/kg/day improves symptoms and biochemistry. Cholestasis and steatorrhoea may cause vitamin K deficiency and predispose to post-partum hemorrhage if prolonged prothrombin is not corrected before delivery. The foetus is at increased risk of premature labour, foetal distress and stillbirth, but elective delivery at 37–38 weeks avoids these in almost all cases.
3. ***HELLP syndrome.*** Features are nonspecific and are shared by overlapping syndromes such as hemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. Defining features: (a) Haemolysis (microangiopathic). (b) Elevated ALT and AST (2 to 10 times upper limit of normal). (c) Low platelets < 100,000 × 10^9/L. HELLP syndrome occurs in the setting of preeclampsia, with weight gain and oedema, hypertension and tenderness over the liver. Early delivery is helpful, though the condition may progress or develop *de novo* post-partum peaking at about 48 hours after delivery.
4. ***Acute fatty liver of pregnancy*** is most common in first and multiple pregnancies. Onset is confined to the third trimester, with vomiting, upper abdominal pain, anorexia and malaise. Early laboratory findings include hyperuricemia and normoblasts on blood film. Later disseminated intra-vascular coagulation, leucocytosis, hypoglycemia and hyperammonemia develop and progress to fulminant liver failure.
5. ***Ovarian hyperstimulation syndrome*** is caused by fertility treatment. Ascites may require drainage, and correction of haemoconcentration is vital.
6. ***Other liver diseases occurring during pregnancy.***

   Gallstone formation is increased particularly in association with obstetric cholestasis.

   Budd-Chiari syndrome may be seen when the heightened thrombotic tendency unmasks risk factors.

   Hepatitis E has a high mortality in pregnancy.

13. DRUG-INDUCED LIVER DISEASE

Drug-induced liver disease may be immunologically mediated or caused by direct toxicity.

Manifestations of drug-induced liver disease can be varied as given in Table 45.

Peliosis hepatitis—Development of diffuse vascular lakes within the liver due to intake of androgens or oestrogens. The condition may predispose to acute hemorrhage within the liver or intraperitoneally. Another predisposing cause is vinyl chloride. Some cases occur spontaneously. The condition predisposes to angiosarcoma.

14. LIVER TRANSPLANTATION

Indications of liver transplant are listed in Table 46.

Table 47 lists contraindications for liver transplant.

COMPLICATIONS

Graft rejection is confirmed by liver biopsy. Acute rejection responds to high-dose corticosteroids. Chronic irreversible graft rejection typically develops during first year post-transplantation, and is associated with progressive jaundice. Histological features include degeneration of interlobular bile ducts (vanishing bile duct syndrome) and small artery occlusion by lipid-laden macrophages.

Opportunistic infection

- Fungal infection
- Cytomegalovirus (CMV) infection

Recurrent liver disease

- Viral hepatitis
- Primary biliary cirrhosis

Table 45: Manifestations of drug-induced liver disease

Abnormality	*Causative drugs*
• Acute hepatitis	Paracetamol, aspirin, isoniazid, halothane, penicillins, first-generation cephalosporins, allopurinol, cyclophosphamide, vincristine, furosemide, hydralazine, dantrolene, methyldopa, phenytoin, monoamine oxidases, co-amoxiclav
• Acute cholestasis	Chlorpromazine, gold, penicillamine, oral contraceptive pill, androgenic steroids, rifampicin, erythromycin, nitrofurantoin, azathioprine, cyclosporine, propylthiouracil, captopril
• Mixed hepatitis and cholestasis	Sulphonamides, penicillins, phenothiazines, tricyclic antidepressants chlorpropamide, diltiazem, diazepam, carbamazepine, colchicine, NSAIDs, carbimazole, flucloxacillin, co-amoxiclav
• Steatosis	
Microvesicular	Tetracycline, valproate, aspirin, zidovudine
Macrovesicular	Methotrexate, alcohol, glucocorticoids
• Steatohepatitis	Alcohol, amiodarone
• Chronic hepatitis	Isoniazid, nitrofurantoin, papaverine, dantrolene, methyldopa, hydralazine, co-amoxiclav
• Chronic cholestasis	Chlorpromazine, amitryptiline, phenobarbital, flucloxacillin
• Phospholipidosis	Amiodarone, perhexiline maleate
• Cirrhosis	Methotrexate, amiodarone, alcohol, methyldopa, vitamin A
• Granulomatous damage	Phenylbutazone, sulphonamides, phenytoin, diltiazem, tolbutamide, nitrofurantoin, aspirin, carbamazepine, procainamide, quinidine, penicillin, sulphonylureas, allopurinol, sulphasalazine
• Neoplasia	Anabolic steroids, oral contraceptive pill
• Vascular injury	Oral contraceptive pill, vitamin A, arsenic, azathioprine, dacarbazine, cyclophosphamide
• Biliary tract disease	Co-amoxiclav, dextropropoxyphene
• Gallstones	Clofibrate, octreotide, oral contraceptive pill
• Vanishing bile duct syndrome	Chlorpromazine

Table 46: Indications of liver transplant

Cirrhosis
Acute liver failure
• Paracetamol overdose
• Hepatitis B
• Hepatitis E
• Drugs is those used to treat TB
Primary biliary cirrhosis
• Serum bilirubin exceeds 100 mmol/l
• Refractory pruritus
Primary sclerosing cholangitis
• Increasing jaundice
• Recurrent symptomatic cholangitis
Chronic HCV infection
• Decline of liver synthetic function
• (Serum albumin < 28 g/L, prothrombin time > 6 seconds)
Alcoholic liver disease
• Liver failure persists despite abstinence
Hepatocellular carcinoma
Rare causes
• Hepatic venous obstruction pregnancy to cirrhosis
• Biliary atesia in babies
• Genetic disorders
• Wilson's disease
• Crigler-Najjar syndrome

Table 47: Contraindications for liver transplant

Absolute
Disseminated malignancy
Uncontrolled sepsis outside biliary tree
Severe cardiopulmonary disease
Chaotic behaviour (e.g. ongoing alcohol or sustained abuse)
Cholangiocarcinoma
Critical illness
Relative
Portal vein and/or mesenteric vein thrombosis
Advanced age (≥ 65)
Pulmonary hypertension (uncontrolled)
HIV infection

- Primary sclerosing cholangitis
- Autoimmune hepatitis
- Genetic hemochromatosis
- Alcoholic liver disease

Bile duct disorder stenosis, obstruction or leak Vascular compromise: (1) Portal vein obstruction (2) Hepatic artery thrombosis (3) Anastomotic leak with intraabdominal bleeding.

15. GALLSTONES

PATHOGENESIS

Physiochemical Factors

- Increased hepatic cholesterol secretion and chronic supersaturation of bile.
- Enhanced cholesterol crystal nucleation in gallbladder bile.

Motility Defects

- Gallbladder motility defects
- Gallbladder stasis
- Intestinal motility defects. Prolonged intestinal transit, longer migrating motor cycles and disrupted motilin release.

Risk Factors for Gallstones

These are listed in Table 48.

Table 48: Risk factors for gallstones

Cholesterol stones
Older age
Female sex
Obesity, metabolic syndrome, high calorie diet
GI motility disorders
Parenteral nutrition (reduces gallbladder motility)
Pregnancy and sex hormones
Drugs: Octreotide, Ceftriaxone
Diabetes mellitus, cystic fibrosis
Surgery (e.g. vagotomy, biliopancreatic bypass)
Pigment stones
Cirrhosis
Diseases of terminal ileum

CLINICAL FEATURES OF GALLSTONES AND COMPLICATIONS

a. **In the gallbladder**

1. ***No symptoms*** (Silent gallstones)
2. ***Biliary colic—***Due to contraction of gallbladder against a stone impacted in common bile duct. This gives rise to midline or right hypochondrial pain, at times associated with vomiting but generally without fever or systemic upset. Upper abdominal tenderness may be present.
3. ***Acute cholecystitis***

   Symptoms—(a) Pain – Type: *Distension pain* giving rise to a deep, central poorly localised pain. *Peritoneal pain* with overlying skin tenderness and muscle rigidity in right hypochondrium. *Referred pain* radiating to right scapular region. *Digestive tract pain* causing abdominal colic, nausea and flatulence without vomiting.

Signs:

(i) *General*—Include fever with often chills at onset, and tachycardia.

(ii) *Local*—(a) Tenderness and muscle guarding in right upper quadrant. (b) Palpable mass – of globular shape below right costal margin and moving on inspiration may be felt. (c) Murphy's sign – Patient complains of pain on taking a deep breath while the examiner's hand is pressed below the right costal margin. (d) Abdominal distension – may occur and if marked simulates intestinal obstruction. (e) Boas sign – Area of hyperaesthesia over right subscapular region.

Investigations:

1. *Leucocyte count* raised with increased polymorphs.
2. *Radiograph*—Plain film of the abdomen may reveal radio-opaque gallstones or soft tissue mass in region of GB.
3. *Ultrasonography* is the most commonly used method of detecting stones (Fig. 14). Stones must be greater than 1–2 mm in diameter to be seen.

   It is unable to distinguish between cholesterol and calcified stones.
4. *Oral cholecystography* identifies radiolucent stones. It is useful in determining gallbladder contraction and cystic duct patency, and identifying anatomical abnormalities of the gallbladder.

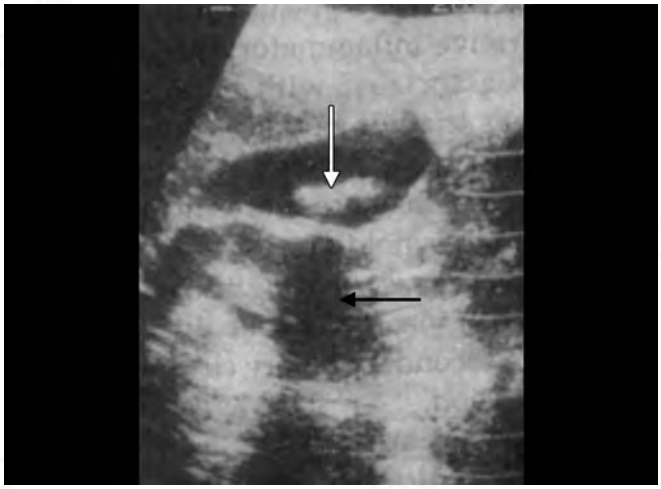


Fig. 14: Ultrasonography showing gallbladder stone (white arrow) with its acoustic shadow (black arrow)

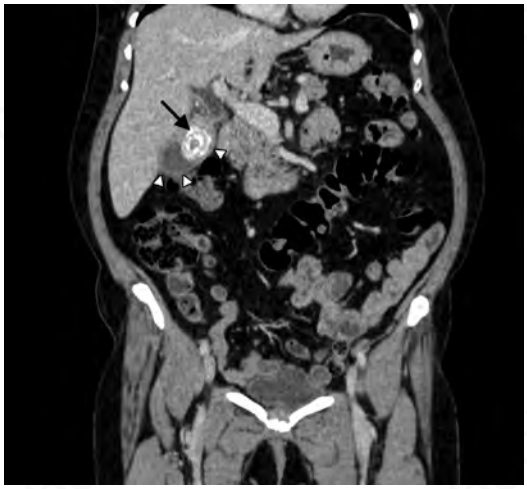


Fig. 15: CT abdomen Showing large single gallstone (arrow) with thickened gallbladder (arrow heads)

5. *CT* is more sensitive in identifying gallstone calcification than plain radiology.

   It is required in selection of patients for non-surgical therapy (Fig. 15).

6. *Other investigations* used in complicated gallstone disease include ERCP for common bile duct stones, LFTs for acute cholecystitis, serum amylase levels for acute pancreatitis.

Management:

1. *Diet*—Nothing by mouth for first 24 hours, or till nausea and vomiting have abated.
2. *Broad spectrum antibiotics*—Parenterally to prevent peritonitis, cholangitis and septicaemia.
3. *Special measures*—(a) Local heat to abdomen. (b) 5% glucose saline intravenously. (c) TPR 2 hourly. (d) Examine abdomen every 2 hours to follow changes in tenderness, rigidity, and character of any palpable mass. (e) Total and differential WBC count. (f) Gastric suction if persistent vomiting.
4. *Surgery*—Cholecystectomy within 2—3 days of the onset of symptoms shortens total hospital stay and avoids incidence of repeated attacks of waiting period of delayed 'cold' cholecystectomy.
5. ***Chronic cholecystitis*** may follow repeated attacks of biliary colic or present with abdominal distension or epigastric discomfort sometimes relieved by belching, nausea triggered by fatty food and a dull ache in right hypochondrium, epigastrium and right subscapular region. There is localised tenderness in right hypochondrium and positive Murphy's sign.

b. **In bile ducts**

1. ***Biliary colic with transient jaundice—***Due to migration of small stones into the common bile duct and ejection through the papilla of Vater.
2. ***Acute pancreatitis—***Due to probably reflux of bile into pancreatic duct through a common channel in ampulla of Vater.
3. ***Obstructive jaundice—***From impaction of stone in common bile duct.
4. ***Cholangitis:***

   (a) *Pyogenic cholangitis*—Acute suppurative or non-suppurative inflammatory process in biliary system associated with biliary obstruction. Charcot's triad of jaundice, upper abdominal pain and high fever with rigors. Added presence of bacteraemia and mental stupor constitute Reynold's pentad.

   (b) *Chronic recurrent cholangitis*—May occur in presence of incomplete bile duct strictures and result in secondary biliary cirrhosis and portal hypertension.

MANAGEMENT OF GALLSTONES

Surgical treatment—Laparoscopic or open cholecystectomy is the only radical procedure for symptomatic gallstones.

Non-surgical treatment

1. ***Oral litholytic treatment***—Bile acids Chenodeoxycholic acid 10–12 mg/kg/day, and Ursodeoxycholic acid 10–12 mg/kg/day, alone or in combination (using one half of the dose of each) is suitable for radiolucent small stones (<10 mm in diameter). Pigment stones are not responsive to medical therapy. The whole dose should preferably be taken at bed time. Side effects – Chenodeoxycholic acid: diarrhoea and hypertransaminasemia. Ursodeoxycholic acid: gallstone calcification resulting in treatment failure.
2. ***Contact dissolution treatment***—Percutaneous transhepatic gallbladder puncture followed by application of methyl-butyl ether (powerful cholesterol solvent) directly to the stones. Any number and size of stones can be treated. Complete dissolution is usually achieved within a few hours. Side effects – Post-puncture severe abdominal pain and nausea, erosive duodenitis and biliary peritonitis.
3. ***Extracorporeal shockwave lithotripsy (ESWL)***—Fragments the stones using focussed sound waves; the fragments are subsequently dissolved by bile acid therapy. The procedure is suitable for patients with up to three stones of diameter 10–30 mm. Side effects – Biliary colic, haemobilia and pancreatitis.

Recurrent stones—are radiolucent and smaller, and can be redissolved with bile acids if detected early.

16. PANCREATIC DISEASE

ACUTE PANCREATITIS

Acute pancreatitis is characterized by sudden, severe abdominal pain and a varying degree of systemic upset.

Causes

Causes of acute pancreatitis are enumerated in Table 49.

Table 49: Causes of acute pancreatitis

• Gallstones
• Alcohol
• Drugs: Tetracyclines, oestrogens, azathioprine, thiazides, valproic acid, corticosteroids, organophosphorus poisoning
• Infections: Viral hepatitis, mumps, toxoplasmosis, roundworms
• Iatrogenic: ERCP
• Metabolic conditions: Hypertriglyceridemia, kidney failure, post-kidney transplantation, hypercalcemia, acute fatty liver of pregnancy
• Trauma blunt and penetrating
• Hereditary
• Scorpion sting
• Idiopathic

Pathogenesis

Acute pancreatitis is caused by various insults to the pancreas leading to local injury, activation of pancreatic enzymes and in some cases, activation of the systemic inflammatory response syndrome (SIRS). This manifests as signs of organ failure or dysfunction and of sepsis. Local inflammatory changes in the pancreas, perhaps combined with systemic circulatory effects, lead to areas of necrosis of pancreatic tissue.

Clinical Features

- Pain – usually epigastric radiating to the back
- Vomiting
- Dehydration
- Epigastric tenderness
- Confusion (due to hypoxia)
- Jaundice (10–20%)
- Discoloration of flanks (Grey-Turner sign) and/or Discoloration of periumbilical area (Cullen's sign). Both these signs indicate severe necrotizing pancreatitis.

Diagnosis

(a) Point-of-care urine Trypsinogen -2 test. Good sensitivity and specificity and can be used at the bed side.

(b) In such cases CT should be performed to confirm the diagnosis.

Serum amylase and serum lipase elevated three fold or more. Serum amylase value tends to be normal in 3–7 days even in continuous presence of pancreatitis while serum lipase takes 7–14 days.

Management

Immediate treatment—Patient must be fitted with a face mask and given oxygen until there is no danger of organ failure. Simultaneously, fluid replacement with a mixture of crystalloid and colloid to restore circulating volume and maintain urine output. These measures help to limit or prevent organ failure.

Nutritional management: Enteral therapy is started after 2–3 days of admission. Enteral therapy is preferred over total parenteral nutrition as (1) Enteral feeding maintains gut barrier integrity, (2) Prevents bacterial translocation, (3) Less expensive and (4) Less complications.

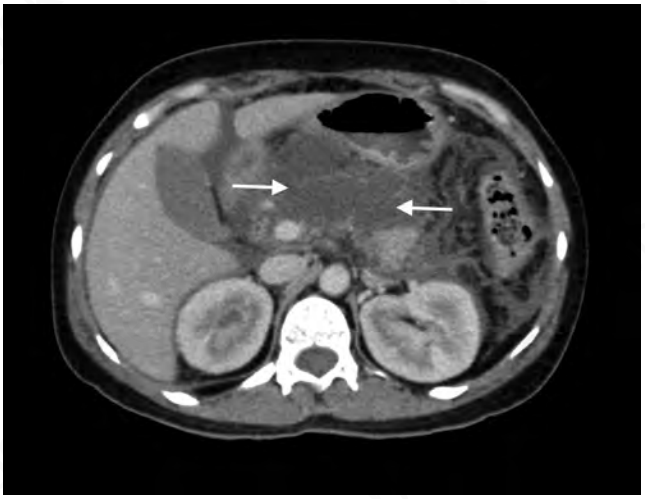


Fig. 16: CT abdomen showing acute necrotising pancreatitis with large oedematous pancreas (arrows)

Further assessment—It can be undertaken once resuscitation has begun. (a) LFTs in first 24 hours indicate a likely biliary cause (raised transaminases or bilirubin). (b) Abdominal ultrasonography reveals any stones in GB. (c) CT may be helpful when there is doubt about the diagnosis, but it is preferable to wait 7–10 days after onset of symptoms for detection of pancreatic necrosis (Fig. 16).

Intervention can be in three forms:

(a) *Treatment to remove the cause:* ERCP for gallstones within 48–72 hours of admission to hospital. Endoscopic sphincterotomy should be performed in all patients undergoing ERCP.

(b) If secondary to alcohol consumption or medication (valproate, pentamidine, azathioprine, oestrogens, cytosine arabinoside, and possibly furosemide or corticosteroids) patient should avoid these agents in future.

- *Preventive treatment:* Early enteronutrition is safe and preferred to parenteral nutrition. Patients with mild pancreatitis can be allowed to drink freely from admission.
- *Prophylactic antibiotics* in patients with predicted severe pancreatitis including evidence of pancreatic necrosis. There is no role of prophylactic antibiotics in necrotizing pancreatitis. If patient appears septic then broad spectrum antibiotic started till culture report awaits. In case of negative culture reports antibiotics should be stopped.
- *Surgical treatment* may be necessary for complications such as pancreatic necrosis or pseudocyst.

Late Complications

Pseudocysts can cause abdominal pain, anorexia or gastric symptoms, can often be palpated, and are diagnosed by ultrasonography or CT.

Abscess presents like pseudocyst with additional symptoms of sepsis. Imaging, diagnostic aspiration and culture confirm the diagnosis.

Internal fistulas are uncommon but can cause pleural effusion and persisting ascites.

CHRONIC PANCREATITIS

Chronic pancreatitis is a progressive, irreversible inflammatory disease. The dominant symptom is usually upper abdominal pain, which can be incapacitating. As the disease progresses, exocrine insufficiency (manifested as weight loss and steatorrhoea) and/or endocrine insufficiency (diabetes mellitus) become more common.

Aetiology

1. ***Chronic calcifying pancreatitis*** (CCP)

   Alcohol is the major cause, the risk related to duration of drinking and amount consumed. CCP is more likely to develop in individuals with a high-fat, high-protein diet. Most patients are men between ages of 40 and 50 years.

   Idiopathic pancreatitis is equally common in men and women. There is bimodal age distribution. In contrast to alcoholic CCP, progression to diabetes and steatorrhoea is delayed.

   Nutritional pancreatitis presents in childhood with equal sex distribution. Malnutrition and casava content of the diet have been implicated. Recurrent abdominal pain is the dominant symptom.

   Hereditary pancreatitis is uncommon. Mutations in the cationic trypsinogen have been identified. It is an autosomal dominant condition that begins in childhood and is a significant risk factor for pancreatic cancer (Fig. 17).

   Patients with hyperlipidaemia or hyperparathyroidism commonly present with acute pancreatitis, but some develop CCP.

2. ***Chronic obstructive pancreatitis*** is less common than CCP:
   - Tumors of ampulla and pancreas (mostly malignant)
   - Cystic lesions—Most inflammatory, few congenital or neoplastic.

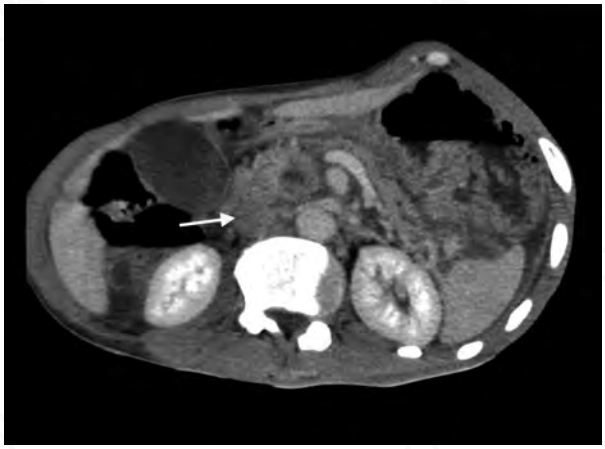


Fig. 17: CT abdomen showing carcinoma of head of pancreas

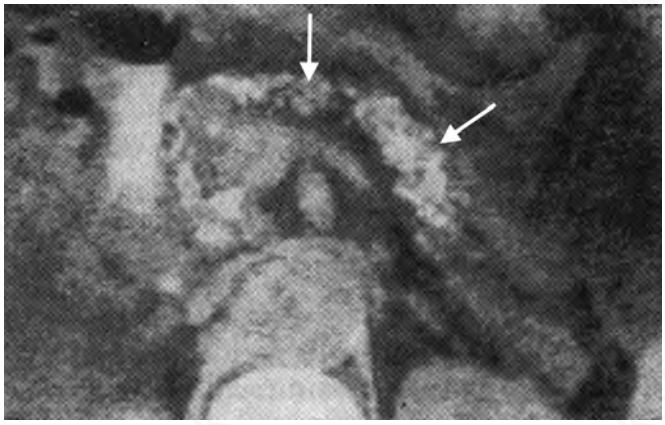


Fig. 18: CT scan showing multiple, discrete, small opacities, diagnostic of calcifying chronic pancreatitis

- Pancreatic duct damage due to acute pancreatitis, resolution of cyst or pseudocyst, or trauma.
- Ampullary stenosis or associated diverticulum.
- Cholelithiasis usually causes acute pancreatitis but some patients have chronic disease.

Clinical Features: Presentation

- *Severe episodic upper abdominal pain,* that radiates to the back. It lasts for hours or days and may be relieved by bending forwards or vomiting. It is often precipitated by large meal or alcohol 12–36 hours previously. Some patients, particularly with idiopathic CCP, experience no pain.
- *Weight loss* with symptoms of pancreatic functional failure (steatorrhoea and diabetes mellitus).
- Some patients with *acute pancreatitis* are diagnosed incidentally at laparotomy or after finding of pancreatic calcification.
- *Complications of the disease* may be presenting feature e.g. epigastric mass from pseudocyst formation.
- *Obstructive jaundice* may result from common bile duct compression by inflamed head of pancreas.

Investigations

Imaging

Plain abdominal radiograph may show pancreatic calcification.

Ultrasonography shows changes in pancreatic size, shape, echotexture and calcification. Endoscopic ultrasonography allows detailed investigation of difficult cases (notably cystic or mass lesions), and demonstrates small calculi not seen by conventional ultrasound.

CT scan—It is initial modality of choice. **I**t shows diffuse calcification, dilated ducts and atrophic pancreas. **CT** (Fig. 18) is less operator dependent and is not affected by bowel gas.

ERCP is the 'gold standard' investigation. Pancreatography demonstrates stenosis or disruption of pancreatic duct, variant duct anatomy and connections to cystic lesions. Cholangiography shows choledocholithiasis and ampullary or common bile duct stenosis.

Magnetic resonance cholangiopancreatography provides information about ductal and vascular structure and function. Uses include evaluation of tumors and cystic lesions, follow up of pseudocysts and stents, and when ERCP has failed to diagnose.

Biochemical investigations—There is no reliable biochemical test for chronic pancreatitis.

Serum enzymes amylase, isoamylase, trypsin and lipase levels may be elevated during an exacerbation, but are often normal. An abnormally low serum level is specific confirmation that steatorrhoea is of pancreatic origin.

Exocrine Function Test

(a) Secretion capacity: (i) Chymotrypsin or elastase in the stool. (ii) pancreozymin - secretin test has good specificity and sensitivity. The test requires intubation of the duodenum. After stimulation with pancreozymin and secretin, enzyme secretion and volume are measured. The test is positive if >50% of glandular tissue is destroyed.

(b) Digestive capacity: Tubeless pancreatic function test NBT-PTA test and pancreo lauryl test, which are based on the detection of degradation products released by

pancreatic specific enzymes after oral intake, and are resorbed from the intestine and excreted in urine.

Qualitative stool fat determination - In steatorrhoea fat content of stool >7g/24 hour.

(c) Endocrine function test: Oral glucose tolerance test is impaired.

Pancreatic biopsy. Percutaneous ultrasound-guided or CT - guided biopsy using automated device (biopsy gun) is safe and reliable technique to obtain a histological sample. It is used to determine the nature of pancreatic mass lesions, and in whom there is a strong suspicion of chronic pancreatitis if other investigations have not helped.

Management

Control of Pain

Nonsteroidal analgesics are preferred but most patients with severe pain require oral narcotic analgesics.

Abstinence from Alcohol

Steatorrhoea—Pancreatic enzyme supplements enteric coated. A few patients also require H_2 receptor antagonists or dietary fat restriction.

Diabetes—may be controlled using diet or oral hypoglycaemic agents. Patients who require insulin are prone to hypoglycaemic episodes.

Endoscopic therapy and ERCP—Patients are first screened by fluoroscopy and MRCP to assess the morphology of the duct and see the location, size and distribution of stones. Patients who are suitable for endotherapy are first subjected to intensive ESWL sessions for stone pulverization followed by ERCP and stone clearance.

Antioxidant therapy—Micronutrient supplementation with selenium, methionine and vitamins A, C and E, since evidence suggests that oxidative stress is an important factor in pathogenesis of pancreatitis, regardless of the aetiology.

Surgery—Suitability for surgical approach – Patients who have a complete distal pathology in the head, have an inflammatory head mass, those who have predominantly tail stones and those who have an atrophied gland with severe pain are most suitable for surgical intervention (Head coring, bypass or resection).

Chronic tropical pancreatitis is a juvenile form of pancreatitis affecting usually young males, and not related to intake of alcohol.

Abdominal pain – In epigastric area radiating to back and precipitated by large meal. Associated features parotid gland enlargement, under nutrition, malabsorption and steatorrhoea due to pancreatic exocrine deficiency. Diabetes mellitus.

Tr. Same as chronic pancreatitis. Insulin for control of DM.

AUTOIMMUNE PANCREATITIS

It is disorder with autoimmune pathology and characteristic laboratory, histological and morphological features. It is associated with other disorders of presumed autoimmune etiology and this has been termed IgG4 systemic disease.

It has 2 types:

1. Type 1: Pancreas is involved as part of systemic IgG4 disease. On histopathology, there is lymphoplasmacytic infiltration with IgG4 positive cells.
2. Type 2: It is without IgG4 positive cells and systemic involvement

Clinical Features

Abdominal pain, weight loss, new onset diabetes, steatorrhoea.

Clinical features of associated systemic IgG4 diseases-Sjögren's syndrome, rheumatoid arthritis, cholangitis, Mikulicz's disease, sialadenitis, autoimmune thyroiditis, ulcerative colitis, tubulointerstitial nephritis.

Investigations

1. Alkaline phosphates elevated out of proportion to minimally elevated aminotransferase.
2. Elevated IgG4 levels.
3. Autoantibodies seen like ANA, rheumatoid factor.
4. CT scan reveals focal enlargement, diffuse enlargement and distinct enlargement of pancreatic head.
5. ERCP or MRCP reveal diffuse irregular narrowing of pancreatic duct.

Treatment

These patients respond well to systemic steroids. Prednisone is started at the dose of 40 mg/day for 2–4 weeks then as per patient response it is tapered 5 mg/week.

Response is monitored with clinical improvement, decrease in alkaline phosphatase level and IgG4 levels and serial changes in imaging.

Type 1 patients tend to relapse in those patients use of azathioprine has shown improvement. Other agents like rituximab, cyclophosphamide, cyclosporine have been successful in small group of patients.

CHAPTER 3

The Respiratory System

1. INVESTIGATIONS OF RESPIRATORY DISEASE

Imaging in chest disease

CHEST RADIOGRAPHY

Radiographic Projections

Erect radiographs are preferred to supine radiographs because – (a) Lungs are more expanded, allowing easier assessment of pulmonary and mediastinal structure. (b) Air-fluid levels are detectable. (c) A gravitational gradient in vessel size from large at base to smaller at apex is present. A radiograph can be identified as erect if the gastric air bubble (though not always present) lies under the left hemidiaphragm.

Lateral views may be useful for – (a) Clarifying the nature of opacities seen on PA film. (b) Localizing lesions. (c) Detecting lesions lying behind heart or diaphragm. (d) In patients presenting with haemoptysis and a normal PA radiograph.

Alteration in Normal Anatomy

Lungs– *Zones:* For sake of convenience the lung fields are divided into upper (above anterior end of 2nd rib), middle (between anterior ends of 2nd and 4th ribs) and lower (below anterior end of 4th rib).

Observations – Both lung fields should be compared, they should be equally lucent at equivalent sites. Apices, costo-phrenic and cardio-phrenic angles should be clear. Vessels in upper zone are thinner than those of a similar generation in lower zones.

Reversed relationship is an important sign of raised pulmonary venous pressure or basal lung pathology e.g. pulmonary emboli or fibrosing alveolitis. The horizontal fissure is of hairline thickness and extends horizontally or slightly downwards from 1 cm below right hilar point (point at which superior pulmonary vein and pulmonary artery cross) to the chest wall. Displacement indicates a possible volume change in the right chest.

Diaphragm– Both the hemidiaphragms have a smooth curve, the right hemidiaphragm being higher by up to 3 cm, than the left. The curve is flattened in generalised emphysema. Elevation of the diaphragm can be unilateral or bilateral.

Chest wall– Ribs must be examined by scanning up and down. Main abnormalities include fracture, notching, evidence of surgery and change in structure such as sclerosis or destruction. Crowding of ribs seen in case of lung volume loss, e.g. fibrosis, post-tuberculosis sequelae and increased spacing between ribs seen in diseases like emphysema or compensatory inflation in response to lung volume loss on opposite side.

Mediastinum* and *heart– The mediastinum envelope is formed by borders of various structures, (enlargement of which causes local prominence of the appropriate segment).

Lung hila– Radiographically, the hila consist of vascular structures (arteries and veins). Each hilum should be approximately equal in size and of same density. *Hilar abnormalities* can be – (a) Change in size – usually enlargement of normal component e.g. enlargement of pulmonary artery in case of pulmonary hypertension. (b) Reorientation of normal components e.g. with collapse of a lobe. (c) Appearance of a mass e.g. lymphnode enlargement or carcinoma.

Digital chest radiography—Conventional requires exposure of a film to X-rays. In picture – achieving communication systems (PACS), pictures are taken using digital techniques that do not require formation of an image on a film. The information derived can be reimprinted onto a reusable photostimulable plate. The digital image generated can be printed onto film or stored in a computer system, from which it can be transmitted to wards and outpatients. The images can be manipulated, allowing magnification, measurement and contrast manipulation, and stored and recalled for comparison with earlier films.

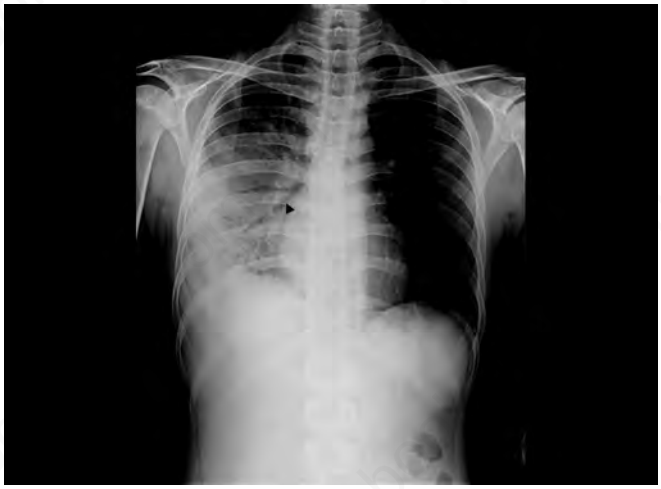


Fig. 1: X-ray chest showing extensive homogeneous white shadowing in the mid and lower zones of right lung with air bronchogram

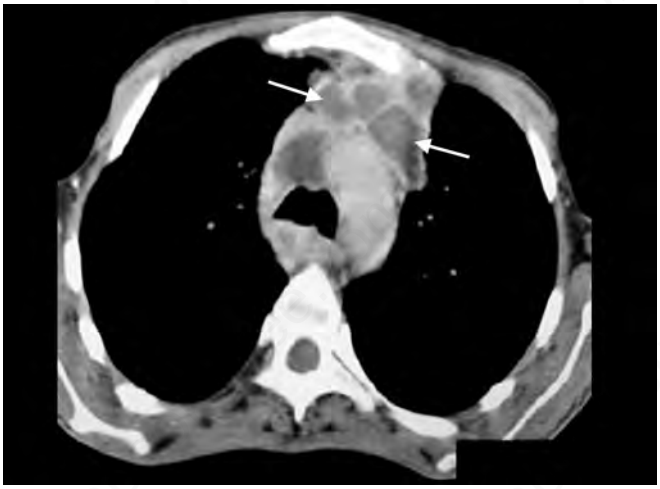


Fig. 2: CT thorax showing caseating enlarged mediastinal tubercular lymph nodes

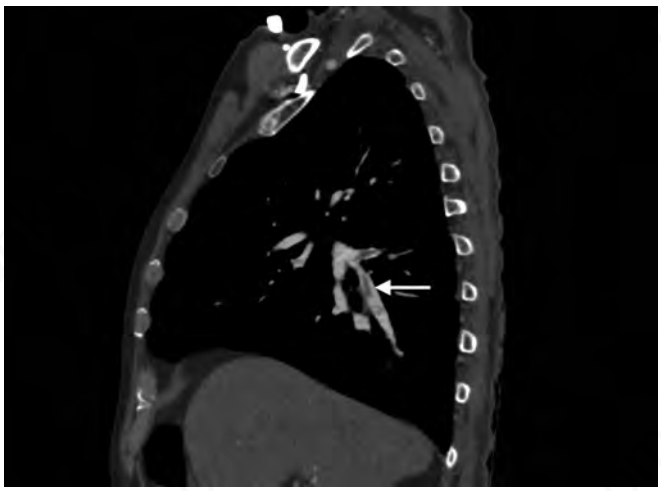


Fig. 3: Pulmonary embolism

The chest radiograph in lung diseases. Basic patterns are:

- Air bronchogram
- Pulmonary collapse
- Pulmonary nodule/mass
- Multiple pulmonary nodules
- Ring shadows and cysts
- Line shadows
- Nodular, reticular honeycombing
- Increased transradiancy

Air bronchogram. The intrapulmonary airways distal to the proximal segmental bronchi are not normally visible on a chest radiograph. When the normally aerated pulmonary parenchyma is replaced by non-aerated tissue, the bronchi and bronchioles become visible as branching, linear lucencies – the air bronchogram, this may occur because the alveoli are filled with fluid or cellular material or because the interstitium expands and compresses the alveolae. The most common causes are pneumonia and pulmonary oedema (Fig. 1).

CT scanning– Its important applications are – (a) Detection and characterization of mediastinal masses (Fig. 2). (b) Staging bronchial carcinoma, assessing spread particularly lymphnodes, and invasion of adjacent structures. (c) Locating and characterizing pleural disease, distinguishing between lung and pleural diseases, e.g. abscess and empyema, staging pleural mesothelioma and assessing chest wall invasion. (d) Assessing the doubtful hilum, distinguishing vessels and masses. (e) Metastatic nodule detection in the lung. (f) The 3-dimensional images obtained by multi detector CT scan (MDCT) can be reconstructed digitally and utilised to generate airways up to sixth or seventh generation, it is called as Virtual bronchoscopy. (g) CT pulmonary angiography, using contrast agent with MDCT, allows visualisation of pulmonary vasculature and helps in diagnosis of thromboembolic diseases upto segmental and subsegmental level. It has added advantage that simultaneous visualisation of pulmonary parenchyma to detect any contributory disease condition (Fig. 3).

High resolution CT (HRCT) scanning is more sensitive and specific in the diagnosis of parenchymal lung disease than conventional radiography. It can sometimes supplant biopsy e.g. in suspected cases of chronic fibrosing alveolitis, asbestosis and lymphangitis.

Ultrasound is useful for imaging pleural disease (both pleural fluid and pleural thickening) and outlining

diaphragmatic regions e.g. subphrenic abscess. It is also used for diagnostic and therapeuric pleural fluid aspiration especially in loculated effusions.

MRI has limited application in the chest. Its major applications include: (a) Imaging of aortic aneurysms. (b) Detection of tumour invasion of chest wall and mediastinum. (c) Distinguishing between tumour and consolidation or post-treatment fibrosis. (d) Assessing posterior mediastinal masses. (e) Distinguishing between nodes and vessels.

Bronchography – Radiography of the lungs after injection of an opaque medium in the bronchi may be indicated for – (a) Unexplained haemoptysis. (b) Bronchiectasis especially prior to surgery. (c) Broncho-pleural fistula. (d) Lung tumors. Contraindication – Recent episode of haemoptysis or severe chest infection.

Positron emission tomography (PET) scanning – It is used to identify malignant lesions of lung depending on uptake and metabolism radiolabelled glucose, [^{18}F]-fluoro-2-deoxyglucose (FDG).

The drawback of test is limited anatomical definition which can be overcome by combining with CT scan. It allows superimposition of PET and CT images and helps in functional plus anatomical mapping.

PULMONARY FUNCTION TESTS

Indications for PFTs

See Table 1 for Indications for PFTs.

Limitations

1. Tests cannot reveal pulmonary disease unless the functions are sufficiently lower over an earlier testing.
2. Tests do not provide anatomical diagnosis but can help localise it to a section of airway or lung.
3. Tests fail to localise disease process except when lungs or lobes are tested separately.
4. Tests must be multiple since no single test can evaluate total abnormality at one time.

Tests for Airway Function—Spirometric Tests and Peak Expiratory Flow

Various tests that are done for airway function and their significance is given in Table 2.

Table 1: Indications for PFTs

• Initial and sequential evaluation of patient, with exertional or paroxysmal dyspnoea.
• Initial and sequential evaluation of a case of known respiratory disease.
• Differential diagnosis of lung disorders.
• Objective assessment of patients with chest problems, e.g. cough, dyspnoea, chest pain.
• Fitness for surgery, particularly on heart or lung.
• Monitoring response to therapy in drug evaluation, e.g. bronchodilators.
• Following course of general disease affecting lung function, e.g. myasthenia gravis, respiratory polio, polyneuritis, Parkinsonism.
• Degree of and disability assessment of occupational lung disease.
• Research purposes.

Table 2: Tests for airway function

Test	*Definition*	*Normal values*	*Comments*
PEF (Peak expiratory flow)	Fastest flow rate that can be sustained for 10 milliseconds at the start of a maximal expiration after full inspiration	300–700 L/minute	Reflects the calibre of airways Dependent on airway diameter and expiratory effort Inexpensive Most useful for monitoring changes in bronchial asthma
VC (Vital capacity)	Largest volume of air expired from full inspiration to full expiration, or inspired by the reverse process	Usual 3–6 L Decreases with age	Reduced in both restrictive and obstructive disorders Correlation with disability in chronic respiratory disorders
FVC (Forced vital capacity)	The largest volume of air that can be delivered by a forced maximal expiration after a full inspiration (TLC = Volume of air in lungs at full inspiration)	As for VC	As for VC
FEV1 (Forced expiratory volume in 1 second)	Volume expired in the first second of forced expiration after a full inspiration	>75–80% of normal VC	Useful indicator of severity of obstructive disease Correlated with maximal exercise capacity
FEV1/VC ratio	Ratio	>70% in males >75% in females Highest in young non-smokers	<70% diagnostic of airflow obstruction (except when VC is high) High (>85%) in lung fibrosis

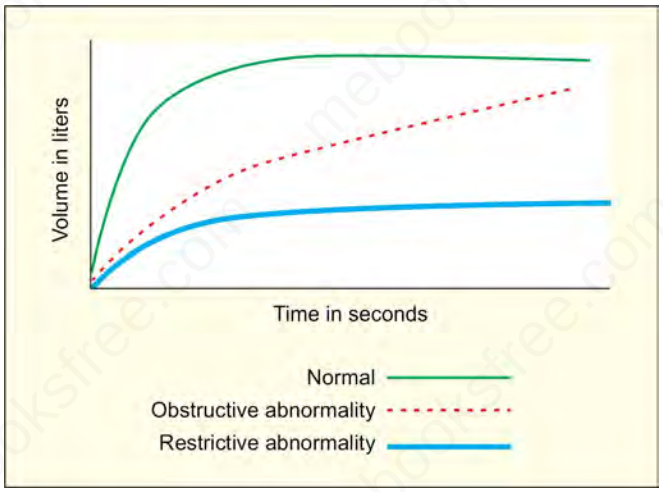


Fig. 4: Interpretation of spirometric data

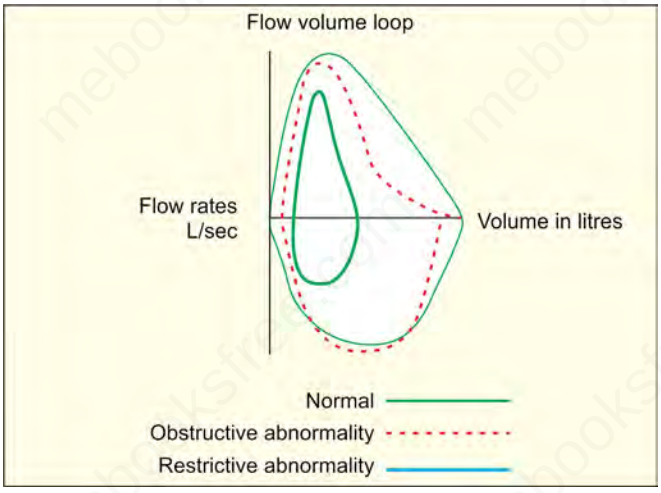


Fig. 5: Flow volume loop (obstruction in COPD - dotted lines)

Improvement (reversibility) of FEV_1 is defined as an improvement in FEV_1 by more than 15% and more than 0.3 litres after administration of salbutamol 200 µg or equivalent by inhalation.

Bronchial challenge studies—Patients with asthma characteristically react to small doses of pharmacological bronchoconstrictors, exhibiting transient decrease in FEV_1 and increase in airway resistance. Most commonly reported measurements are the dose of methacholine or histamine needed to provoke a 20% reduction of FEV_1.

***Volume-time curve* (Fig. 4)** – The FEV_1 depends on good effort in healthy individuals, because the rate at which the lungs empty is determined by the elastic recoil of the lungs and the positive thoracic pressure applied round them by the expiratory muscles. In patients with pulmonary emphysema with reduced elastic recoil and very collapsible airway, FEV_1 is low even when the airways are patent.

***Flow volume curves* –** The term refers to the tracing (a triangular shaped envelop) obtained when a maximal forced expiration is followed immediately by a forceful maximal inspiration (Fig. 5). It is the recording, during spirometry, of expiratory flow plotted against volume. In healthy individuals, the maximal expiratory flow rate decreases steadily throughout forced expiration; as the lungs empty, the airways diminish in size. This representation of maximal flow is useful demonstration of *Small airways disease* – Reduction of expiratory flow during middle of forced expiration, which may be present even when FEV_1 and FVC are normal.

In emphysema when tracheobronchial collapse occurs, peak flow is relatively well preserved but flow rates diminish early in expiration.

In obstruction of the airways outside the thorax, (glottis, larynx or trachea) flow tends to be constant throughout the first part of expiration rather than decelerating; inspiratory flow is often even lower.

Flow volume loop is a graphic expression of flows of different lung volumes. It helps in identifying variable as well as fixed upper airway obstruction (UAO) at various levels. Patients presenting with obstructed main bronchus show 'biphasic flow volume loop' or 'two can effect' due to slow emptying and filling of the affected lung.

A plateau of the inspiratory and expiratory curves suggests large-airway obstruction in extrathoracic and intrathoracic locations, respectively.

M***easurement of static lung by closed circuit helium dilution*** – Patient breathes from spirometer known volume containing about 10%, helium 21% oxygen and nitrogen. Oxygen is added and carbon dioxide removed to maintain a constant volume of gas in the spirometer at the end of each breath. The concentration of helium is measured continuously; the patient rebreathes until the helium concentration remains constant as a result of equilibration with the gas in the lung.

Interpretation

- Restrictive (fibrosing alveolitis): FRC (functional residual capacity), RV and TLC are low, tidal volume often reduced.
- Obstruction (chronic airflow obstruction) – TLC preserved because of increase in RV.
- Airflow obstruction and lung fibrosis: Mixed.

Assessment of reversibility with aerosolized bronchodilators. Significant reversibility is considered to be an increase

in FEV_1 of 200 ml and 12% after 15 minutes of bronchodilator therapy. Bronchial asthma shows good reversibility.

TESTS OF PULMONARY GAS EXCHANGE

The extent of CO gas transfer D_LCO depends on the pulmonary capillary blood volume and the matching between the distribution of ventilation and perfusion of the lungs.

Methods – In the single breath method the patient breathes out to RV, then inspires a gas mixture of helium and CO in air, to TLC. This is held in the lungs for 10 seconds, then the patient slowly exhales. An initial volume of 750 mL (equivalent to the dead space) is discarded, then a sample of expired gas is collected and analysed for alveolar concentrations of helium and carbon monoxide.

The size and integrity of the gas exchanging surface may be assessed using the carbon monoxide transfer factor D_LCO, which is usually measured during 10 seconds of breath holding after full inspiration from RV to TLC. Additional information can be obtained from the transfer coefficient D_LCO volume of air in the lungs during the breath-hold).

Interpretation

D_LCO depends on alveolar function, provided that:

- The airways are normal and allow the inhaled gas to reach the whole lung.
- The concentration of Hb in the blood is normal
- Thickness of the alveolar capillary barrier

D_LCO transfer coefficient is useful in following situations:

- In investigation of breathlessness. Low D_LCO strongly suggests disease at the alveolar level (e.g. interstitial lung disease, pulmonary vascular disease).
- In sarcoid and occupational lung diseases and in conditions characterized by widespread nodules on chest radiography, D_LCO and transfer coefficient reflect the severity of alveolar damage.
- In pleural and chest wall disease, a high transfer coefficient suggests there is no severe underlying lung disease, low values suggest associated alveolar destruction.

Note: Pulmonary plethora, recent pulmonary hemorrhage and polycythemia cause high (D_LCO) Isolated reduction in D_LCO with normal lung volumes in patients of dyspnoea is suggestive of pulmonary hypertension.

ARTERIAL BLOOD GAS ANALYSIS

Arterial blood gas analysis is useful for – (a) Detection of hypoxemia and hypercapnia. (b) Management of respiratory failure. (c) Care of the ventilated patient. (d) Detection of abnormalities of acid-base balance.

Method – Arterial samples can be taken from the radial artery. Whenever possible, blood sample must be taken while patient is breathing room air.

Arterial PCO_2 ($PaCO_2$) – Normal 40 mm Hg (about 5 kPa) ± 12%.

Arterial PO_2 (PaO_2) varies more widely (80–120 mm Hg, 10–16 kPa).

Interpretation

- Alveolar PaO_2 is high during hyperventilation and low in ventilatory failure.
- In healthy individuals, PaO_2 is 10–20 mm Hg less than PAO_2. Greater differences indicate ventilation/perfusion mismatch.
- The alveolar-arterial PO_2 difference may be calculated from the alveolar air equation:

  PAO_2 = inspired PO_2-$PaCO_2$ / R, where R is the ratio of carbon dioxide output to oxygen consumption.

Three rules of thumb follow from this:

- If $PaO_2 + PaCO_2 < 120$ mm Hg (16 kPa) when breathing air, pulmonary gas exchange must be abnormal.
- If $PaO_2 + PaCO_2 >$ inspired PO_2, the patient must have recently breathed a greater concentration of oxygen.
- In normal lungs, PaO_2 (in mm Hg) ^{3} F% $O_2 \times 5$ mm Hg and PaO_2 (in kPa) ^{3} F% $O_2 \times 0.75$ kPa, where F% O_2 is the inspired concentration of oxygen.

Arterial oxygen saturation (SaO_2) may be monitored indirectly with an accuracy of ±2.5% using pulse oximetry. Haemoglobin is 95±2% saturated with oxygen at normal PaO_2. SaO_2 declines to 90% when PaO_2 is about 60 mm Hg (8 kPa), this is a clinically important cut-off point associated with the onset of a noticeable ventilatory stimulus and impairment of cerebral and tissue function in non-acclimatised individuals.

Patients with diseases that cause ventilation perfusion mismatch or shunt physiology have an increased gradient between alveolar gas and arterial blood oxygen tension (A-a) DO_2 at rest.

Arterial blood gas testing also allows the measurement of arterial PCO_2. Hypercarbia can accompany severe airway obstruction (e.g. COPD) or progressive restrictive physiology, as in patients with neuromuscular weakness.

Presentations Suggestive of Respiratory Muscle Weakness

Clinical Constellations

- Unexplained dyspnoea (particularly if combined with orthopnoea or dyspnoea in water)

Table 3: Causes of respiratory muscle weakness

Nerve
Acute
Guillain-Barré syndrome
Organophosphate poisoning
Poliomyelitis
Chronic
Motor neuron disease
Neuralgic amyotrophy (idiopathic and familial)
Trauma (e.g. iatrogenic, road traffic accident)
Hereditary sensorimotor neuropathy
Toxins (e.g. lead)
Drugs (e.g. vincristine)
Porphyria, diabetes mellitus
Lymphomatous/malignant infiltration
Neuromuscular junction
Acute
Botulism
Envenoming, shellfish poison
Drugs with neuromuscular blocking effects (as main effect or side effect)
Chronic
Myasthenia gravis
Lambert-Eaton syndrome
Muscle
Acute
Biochemical disturbance (e.g. hypokalemia)
Periodic paralysis
Chronic
Muscular dystrophies
Myopathy
Acid maltase deficiency
Hypothyroidism

- Chronic respiratory failure (likely to be accompanied by symptoms of nocturnal hypoventilation or hypercapnia)
- Difficulty weaning from mechanical ventilation in the absence of recognized cardiac or pulmonary cause (likely to have low oxygen requirement and low airway pressures, perhaps with difficulty triggering the ventilator)

Recognized Risk Factors

- Known neuromuscular disease (Table 3)
- Clinical features suggestive of neuralgic amyotrophy
- ICU stay of >1 week, particularly if sepsis, use of corticosteroids or neuromuscular blocking agents.
- Surgical/medical procedure known to carry risk to diaphragm or phrenic nerve.
- Marked electrolyte imbalance

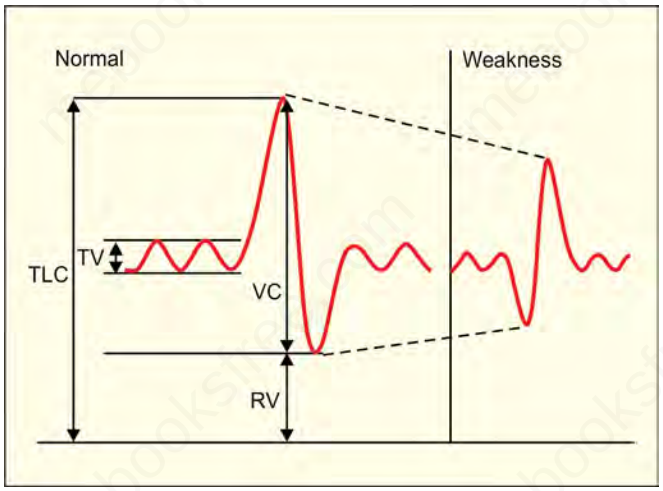


Fig. 6: The effect of respiratory muscle weakness on lung volumes. (TLC= total lung capacity; TV = tidal volume; VC = vital capacity RV = residual volume)

Maintenance of oxygen/carbon dioxide haemostasis requires continuous Figure 3 into and out of the alveolus. In health, inspiration occurs when respiratory muscles contract to generate a sub-atmospheric pressure in the thorax, in contrast, expiration is passive at rest though it can be assisted by expiratory muscle contraction in absence of flow limitation.

A combination of one feature from list A and one from list B is particularly suggestive.

See Figure 6 for the effect of respiratory muscle weakness on lung volumes.

Orthopnoea is a classical symptom. In bilateral diaphragm paralysis, inwards (paradoxical) movement occurs in inspiration.

FIBRE-OPTIC BRONCHOSCOPY

The procedure is usually carried out under sedation and local anaesthesia.

Flexible bronchoscopy enables visual inspection of the airway down to the subsegment, and allows various samples to be easily obtained.

Indications of fibre-optic bronchoscopy are listed in Table 4.

Rigid bronchoscopy is now primarily used for interventional procedures such as removal of foreign bodies, tumour ablation and insertion of stents. It is also used in staging before surgical resection of tumour.

Table 4: Indications of fibre-optic bronchoscopy
Diagnostic
Investigation of symptoms
• Haemoptysis
• Persistent cough
• Recurrent infection
Suspected neoplasia
• Unexplained paralysis of vocal cords or hemidiaphragm
• Stridor
• Localized monophonic wheeze
• Suspicious sputum cytology
• Unexplained pleural effusion
Staging of lung cancer
• Mediastinal tissue diagnosis and staging
Infection
• Identification of organisms (e.g. suspected tuberculosis)
• Evaluate airways if recurrent or persistent infection
• Bronchiectasis/lobar collapse cause
Interstitial lung disease
• Bronchoalveolar lavage for differential cell count and histology
Therapeutic and palliative
• Clearance of mucus plugging
• Foreign body removal
• Palliation of neoplasm
• Endotracheal ablation of tumour and stenting

BRONCHOALVEOLAR LAVAGE (BAL)

Technique

A bronchoscope is wedged in a subsegmental bronchus (right middle lobe is the usual site) and sterile isotonic saline injected and aspirated to obtain lung fluid for examination of cells and fluid content.

Indications

1. *Diagnosis* – (a) Interstitial lung disease. (b) Atypical chest infections (especially in immunocompromised patients). (c) Post transplantation monitoring (diagnosis of infection). (d) Drug toxicity, e.g. amiodarone, bleomycin. (e) Histiocytosis. (f) Lipoid pneumonia. (g) Berylliosis (in vitro test diagnostic). (h) Malignancy (peripheral located tumours).
2. *Therapy* – (a) Alveolar proteinosis. (b) Asthma – especially in ventilated patients with segmental collapse. (c) Idiopathic pulmonary haemosiderosis. (d) Monitoring effect of recombinant α_1 - antitrypsin therapy in patients with a_1 – antitrypsin deficiency.

Table 5: Differential cell counts in diffuse interstitial lung disease on bronchoalveolar lavage	
Lymphocytic excess	*Neutrophil and/or eosinophil excess*
15–40%	Neutrophils
Sarcoidosis Tuberculosis Berylliosis Drugs Organizing pneumonia HIV	4–15%
	Fibrosing alveolitis Cryptogenic fibrosing alveolitis Asbestosis Rheumatological disease
	> 50%
>50%	Infection
Extrinsic allergic alveolitis	80–90%
	Adult respiratory distress syndrome
	Eosinophils >20%
	Pulmonary eosinophilia

Complications

(a) Pyrexia. (b) Bronchospasm. (c) Transient hypoxemia.
Bronchoalveolar lavage. differential cell counts in diffuse interstitial lung disease.
See Table 5.

LUNG BIOPSY

Many diagnostic procedures are available to sample any part of the lung and the choice of technique depends on the type and site of lesion.

Indications

- Investigation of diffuse lung disease, e.g fibrosing alveolitis, sarcoidosis, alveolar cell carcinoma.
- Investigation of solitary pulmonary lesion.
- Investigation of possible infection in an immunocompromised patient.

Diagnostic Methods

1. *Transbronchial lung biopsy* – Under radiographic screening, the flexible biopsy forceps can be advanced to the edge of the lung. Complications: Pneumothorax, minor haemoptysis.
2. *Percutaneous fine-needle aspiration biopsy* – Disadvantage is the small size of tissue samples for cytological examination. Complications – Pneumothorax (higher incidence than transbronchial), minor haemoptysis, rarely air embolism.

3. *Percutaneous Tru-cut needle biopsy*– obtains larger samples for biopsy. Complications similar to other percutaneous techniques with higher incidence of pneumothorax, rarely haemothorax.
4. *Trephine needle biopsy*– Provides larger and less distorted tissue specimens. Complications similar as above but occasionally severe intrapulmonary hemorrhage.
5. *Open lung biopsy* is indicated in cases of chronic diffuse pulmonary shadowing when other less invasive techniques have been unsuccessful. Advantages – (a) It provides higher diagnostic yield. (b) It is more appropriate than transbronchial biopsy or FNAB for difficult cases e.g. pulmonary hypertension, high airway pressure hypoxia or coagulopathy. Complications – Pneumothorax, wound infection.

PULMONARY ANGIOGRAPHY

Indication – Establishing or excluding presence of pulmonary embolism. It is *contraindicated* in chronic pulmonary hypertension, severe cardiac decompensation or respiratory decompensation.

Observation – Presence of constant, intraluminal filling defect or sharp cut-off in vessels greater than 2.5 mm in diameter is diagnostic. Other abnormalities such as oligaemia, vessel pruning or loss of filling of small vessels are non-specific and may occur in pneumonia, atelectasis, bronchiectasis, primary pulmonary hypertension, emphysema.

2. COUGH AND EXPECTORATION

COUGH

Causes

1. *Infections* – (a) Acute – Laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia. Whooping cough. (b) Chronic – Pulmonary tuberculosis, chronic bronchitis, chronic laryngitis, bronchiectasis, lung abscess.
2. *Mechanical irritation* – (a) Inhalation of dust (pneumoconiosis), irritant gases, chemical fumes or pungent smells. Tobacco smoking. (b) Foreign body in larynx or bronchi. (c) Post-nasal drip in chronic sinusitis. (d) Gastro-oesophageal reflux. (e) Compression of air passages – (i) Extramural – Aortic aneurysm, pulmonary neoplasm, mediastinal masses, enlarged LA in mitral stenosis. (ii) Intramural – Bronchogenic carcinoma or adenoma, foreign bodies, bronchospasm (asthma), granulomatous endobronchial disease. (f) Pressure or tension on air passages – Pulmonary oedema, interstitial fibrosis, atelectasis, pericardial effusion, pneumothorax.
3. *Reflex* – From reflex irritation of vagus – (a) Wax in external ear or otitis media. (b) Distention of stomach or rarely of colon. (c) Subdiaphragmatic abscess or liver abscess.
4. *Thermal stimulus* – Inhalation of cold air especially in asthmatics and those with intercurrent infection.
5. *Habit cough* – When a patient has suffered from some prolonged illness in which cough has been a prominent feature, the cough may at times persist as a habit long after the cause has ceased to operate.
6. *Psychogenic cough* – may be a form of obsessional neurosis or co-ordinated tic.
7. *Iatrogenic* - ACE inhibitors, steroid aerosols.

Types of Cough

1. *Dry or unproductive* – Upper respiratory tract infection, early stage of pulmonary tuberculosis, bronchogenic carcinoma, smoker's cough, interstitial fibrosis, bronchial asthma, tropical eosinophilia, pulmonary infarction, etc. Psychogenic or habitual cough.
2. *Wet or productive* – Bronchiectasis, lung abscess, fungal infections.
3. *Paroxysmal* – Bronchial asthma, cardiac failure, whooping cough.
4. *With wheezing* – Bronchial asthma, tropical eosinophilia, chronic bronchitis.
5. *Barking* – Harsh, loud, 'seal-like' cough, paroxysmal or occasional, in hysteria (functional) disturbing to the hearer, but perhaps not to the patient himself or herself.
6. *Nocturnal* in asthma, pulmonary oedema, post-nasal drip in chronic sinusitis, reflux oesophagitis.
7. *Bovine* – (Brassy or gander, or leopard's growl) – due to laryngeal paralysis from involvement of recurrent laryngeal nerve e.g. in aortic aneurysm.
8. *Staccato* – In whooping cough there is paroxysmal cough ending in a whoop.
9. *Croupy* – Harsh, hoarse cough in laryngeal infection.
10. *Hacking* – Short, dry, irritable cough frequently repeated in congestive conditions of pharynx, upper air passages, and smoker's cough.

11. *Suppressed and painful* – In pleurisy cough is suppressed because chest pain is aggravated by coughing (and deep breathing).
12. *Toneless, whispering, aphonic cough* – in destructive lesions of vocal cords, e.g. tuberculous ulcer or neoplasm.
13. *Spluttering* in trache-oesophageal fistula.
14. *Cough related to exertion* – In early LV failure and mitral stenosis.
15. *Cough related to meals* – Suggests hiatal hernia, trache-oesophageal fistula, or oesophageal diverticula.
16. *Early morning cough* with expectoration in bronchiectasis and pulmonary TB.
17. *Nocturnal cough* – LV failure, bronchial asthma, chronic bronchitis, aspiration, post-nasal drip, GERD, oesophageal obstruction, ACE inhibitors.
18. *Recent worsening in case of chronic cough* is a common presenting symptom of bronchial carcinoma.

Complications

1. *Cough syncope* – Prolonged coughing can reduce venous return, impair cerebral blood flow, thus cerebral oxygenation and result in syncope.
2. *Rib fracture* – especially pathological, e.g. in multiple myeloma, osteoporosis and osteolytic metastasis.
3. *Spontaneous pneumothorax* from rupture of emphysematous bulla.
4. *Hernia* – at weak hernial sites.

Treatment

1. *Treatment of cause where possible.* 2. *Cough suppressants* – for dry cough. Diamorphine, methadone, codeine, or pholcodine in form of linctus. Dry cough in bronchial asthma responds to β-agonist inhalation. 3. *Expectorants* – Mucolytic drugs such as bromhexine, guaifenesin, acetylcysteine, carbocisteine reduce sputum viscosity and help expectoration.

Causes of recurrent, persistent cough

Table 6: Causes of recurrent, persistent cough

• Asthma
• Recurrent normal infections
• Prolonged infection (e.g. TB, whooping cough)
• Aspiration (gastro-oesophageal reflux)
• Habit, psychogenic
• Cigarette smoking (active/passive)
• Intrabronchial foreign body
• Suppurative lung disease
• Congenital abnormalities

See Table 6 for causes of recurrent, persistent cough.

EXPECTORATION

Naked Eye Examination

Quantity

1. *Scanty* – Small quantity of sticky secretion usually voided at end of asthmatic attack, in early stages of pneumonia and bronchitis.
2. *Moderate amount* – i.e. about 2 ounces daily in chronic chest complaints like bronchitis and tuberculosis, bronchiectasis, lung abscess.
3. *Large quantity* – Bronchiectasis, lung abscess, chronic bronchitis, cystic fibrosis. Sudden coughing up of large quantity in lung abscess, empyema or subphrenic abscess rupturing into bronchus.

Appearance

1. *Watery* – Due to pulmonary congestion or acute pulmonary oedema, alveolar cell carcinoma or ruptured hydatid cyst where fragments of daughter cysts may be detected.
2. *Mucoid* – Sticky sputum containing increased mucin in acute or chronic bronchitis, asthma, weakened bronchial musculature, pneumoconiosis, early stages of pulmonary TB and sometimes bronchogenic carcinoma.
3. *Mucopurulent* – The sputum is generally mucopurulent and almost all infections of bronchi and lungs give rise to this type of sputum. Such sputum may be nummular or coin like, the sputum when expectorated into fluid taking on the shape of flattened discs, such sputum indicates cavitation of any type. Mucopurulent sputum separates into three layers when collected in a conical glass.
4. *Purulent* – Indicates infection somewhere in the respiratory tract. Large quantities of purulent sputum in bronchiectasis, lung abscess, chronic foetid bronchitis, pulmonary tuberculosis and gangrene of lung.
5. *Colour of sputum* – (i) *Blackish* – due to inhalation of carbon in coal miners, copious black sputum (melanoptysis) may occur when there is breaking down of lung tissue. (ii) *Rusty (or khaki)* – due to altered blood mixed with tenacious sputum in lobar pneumonia. (iii) *Small yellow sulphur granules* – in actinomycosis of lungs. (iv) *Reddish colour* – indicates presence of blood, fresh or altered, depending on the interval between the haemoptysis and production of the specimen. (v) *Frothy pink sputum* – in pulmonary oedema. (vi) *Creamy yellow sputum* – of staphylococcus infection.

(vii) *Sticky brown-to-red sputum* – in Klebsiella (Friedlander's) infection. (viii) *"Currant jelly" sputum* – due to the presence in the sputum of blood tinged lung debris is likely to occur in influenza and bronchogenic carcinoma. (ix) *Dark brown purulent material* – like anchovy sauce in amoebic lung abscess and paragonimus (lung fluke) infection. (x) *Green colour* – (and musty odour) of sputum in pseudomonas infection. Purulent sputum if it has been stagnant as after overnight sleep, may be greenish owing to action of verdoperoxidase derived from neutrophils. (xi) *Blood oyster* – Fresh blood embedded within mucopurulent sputum in tuberculosis. (xii) *Rubbery brown plugs* – Allergic bronchopulmonary aspergillosis. (xiii) *Chalky white* and gummy consistency in pulmonary alveolar proteinosis.

Other Abnormalities

a. *Discrete discs* in a purulent sputum (nummular sputum) suggest cavitation.
b. *Dittrich's plugs* or small caseous masses, greyish yellow in colour and foul smelling in bronchiectasis.
c. *Mucus plugs* may be visible in asthma and the sputum may also appear yellow due to excess of eosinophils.
d. *Curschmann's spirals* (coalescence of granules from disintegrating eosinophils) in asthmatic sputum may be seen by naked eye.
e. *Fibrinous casts* of smaller bronchi may be expectorated in fibrinous bronchitis as grey, white or reddish yellow particles.
f. *Asbestos bodies* due to exposure to asbestos dust.
g. *Calcified bodies* occasionally coughed up in pulmonary alveolar microlithiasis.
h. *Hooklets* of hydatid disease if cyst ruptures into bronchus.

Odour:

A foul odour indicates infection with anaerobes, fusiform bacilli or spirilla and may occur in lung abscess, bronchiectasis, bronchial carcinoma, foetid bronchitis, gangrene lung.

Microscopic Examination

1. *Organised constituents:*
   a. *Fibrinous casts* – Casts of a small bronchus in fibrinous bronchitis, pneumonia during stage of resolution and diphtheritic affection of finer bronchi.
   b. *Bronchial spirals* – Resemble bronchial casts. Faint, translucent, elongated masses, with a delicate white fibre running longitudinally through centre of each spiral. Leucocytes, epithelial cells and Charcot-Leyden crystals entangled in the spiral common in asthma. Sometimes in chronic bronchitis and pulmonary TB.
   c. *Elastic tissue* – Single threads or small bundles indicate destructive process in lung, e.g. abscess of lung, cavitation, bronchiectasis.
2. *Eosinophils* – Presence of eosinophils suggests an allergic process, they are commonly found in asthma and pulmonary eosinophilia.
3. *Animal parasites*– Paragonimus westermani, Entamoeba histolytica, filaria, tinea, echinococcus, ascaris, bilharzia.
4. *Fungi* – Actinomycosis, aspergillosis.
5. *Bacteria* – Tubercle bacillus, pneumococcus, C. diphtheria, H. influenzae, staphylococci and streptococci, etc.
6. *Malignant cells* – May be found in bronchogenic carcinoma.
7. *Foreign bodies* – Due to occupational dusts such as asbestos, silica, cotton flax, etc.

Culture and antibiotic Sensitivity Tests

Culture of fresh sputum is necessary for obtaining a microbial diagnosis of pneumonia, tuberculosis and fungal infections. Appropriate antibiotic sensitivity tests should be performed on all clinically significant isolates.

3. HAEMOPTYSIS

Coughing out of blood includes both blood-stained sputum and frank haemoptysis. Massive haemoptysis is defined as 600–800 mL of blood in 24 hours. See Table 7 for the causes of haemoptysis. Tables 8 and 9 list causes of massive and recurrent haemoptysis, respectively.

Table 10 gives differentiating features between haemoptysis and haematemesis.

INVESTIGATION OF HAEMOPTYSIS

History

(1) *Personal* – (a) Age – In childhood and adolescence: Pulmonary TB, M.S., bronchiectasis main causes. In adults: Pulmonary TB. After 40: TB, bronchial carcinoma, bronchiectasis. Idiopathic haemoptysis occurs almost solely in childhood. (b) Occupation: e.g. cotton mill workers. (2) *Symptoms* – (a) Amount of blood – Haemoptysis from pneumonia or infarct often merely consists of blood streaking of sputum. (b) Haemoptysis immediately preceded by cough indicates origin of bleeding at a level lower than the larynx. (c) Repeated severe haemoptysis without obvious deterioration in bronchiectasis. (d) Repeated haemoptysis over many years with perfect health in-between may suggest adenoma of bronchus. (e) Haemorrhages from other sites in bleeding disorders. (3) *Past history* – (a) Of fever,

Table 7: Causes of haemoptysis

Pulmonary causes

Infections
- Tuberculosis
- Bronchiectasis
- Lung abscess
- Pneumonia
- Aspergilloma
- Parasites (hydatid, flukes)
- Actinomycosis
- Bronchial foreign body

Pulmonary infarction

Tumors
- Bronchial carcinoma
- Bronchial adenoma

Pulmonary hemorrhage
- Idiopathic pulmonary haemosiderosis
- Goodpasture's syndrome
- Systemic lupus erythematosus
- Granulomatosis with polyangiitis
- Microscopic polyangiitis

Trauma
- Pulmonary contusion
- Needle biopsy
- Transbronchial biopsy

Vascular abnormality
- A-V malformation

Cardiovascular disease
- Pulmonary oedema
- Mitral stenosis
- Aortic aneurysm

Blood disorders
- Leukemias
- Haemophilia
- Anticoagulants

Idiopathic

Tables 9: Recurrent haemoptysis

- Bronchiectasis, chronic bronchitis.
- Bronchial adenoma.
- Mitral stenosis, recurrent LV failure.
- Recurrent pulmonary embolism with infarction.
- Telangiectasia.

cough and expectoration in bronchiectasis. (b) Recent operation or phlebitis in pulmonary infarction. (c) Trauma to chest. (d) Tr. of squamous cell carcinoma of lung with Bevacizumab, a vascular endogenous growth factor inhibitor can result in massive haemoptysis. (4) *Family history*– of tuberculosis or bleeding disorder.

Physical Examination

(a) *Upper air passages* – for bleeding gums, epistaxis and superficial erosions of nasopharynx and mouth if small quantities of blood. Often the blood collects in larynx or

Tables 8: Massive haemoptysis

- Pulmonary TB (active or healed)
- Bronchiectasis
- Mycetoma
- Lung abscess
- Lung malignancy
- AV fistula

Table 10: Differentiation from hematemesis

Haemoptysis	Haematemesis
Symptoms and signs of pulmonary or cardiac disease	Symptoms of gastric or abdominal disease
Blood coughed up	Blood vomited
Blood bright red, frothy and mixed with sputum	Coffee ground, mixed with food particles
Relatively small amount	May be large amount
Reaction alkaline	Reaction acid
Sputum rusty next day	Stool tarry next day

trachea and is coughed out early morning. (b) *Heart and lungs* –Common causes of profuse haemoptysis are pulmonary tuberculosis, bronchiectasis, mitral stenosis and bronchogenic carcinoma. (c) *Lymph glands, and enlarged liver and spleen* – Splenomegaly, hepatomegaly, lymphadenopathy, hematomas, petechiae and signs of bleeding from other body areas are suggestive of a generalized haemorrhagic disease.

INVESTIGATIONS

1. *Sputum* – For tubercle bacilli and malignant cells. Rarely spirochetes, or ova of lung fluke.
2. *X-ray chest* – For diagnosis of pulmonary T.B., hilar mass suggestive of carcinoma, pneumonia or pulmonary infarct.
3. *Blood* – Red blood cell count and haemoglobin, bleeding, coagulation and prothrombin time. Measurement of plasma fibrinogen. Precipitating antibodies in Aspergillus fumigatus.

   Renal function tests and urinalysis is done in suspected patients with pulmonary-renal syndrome. If urinalysis shows red blood cells or casts testing of patient serum for antiglomerular basement membrane antibody, antineutrophil cytoplasmic antibody and antinuclear antibody should be considered.
4. *Examination of the larynx* – For evidence of ulceration.
5. *Bronchoscopy* – To exclude foreign body and malignant growth and for diagnosis of bronchiectasis.

Table 11: Mechanisms of lung infection

Mechanism	*Examples*
Aerosols inhalation	*Mycoplasma pneumoniae* *Chlamydophila psittaci* *Legionella pneumophila*
Aspiration of oropharyngeal secretions	*Streptococcus pneumoniae* *H. influenzae* *Anaerobes*
Haematological spread	*Staph. Aureus*
Reactivation of latent microorganisms	*M. tuberculosis* *Pneumocystis jiroveci*

6. *Bronchography* – To establish presence of localised bronchiectasis if sputum repeatedly negative and plain X-ray inconclusive.
7. *Needle aspiration biopsy* – If chest X-ray shows localised intrapulmonary lesion.
8. *Pulmonary angiography* – May show anomaly of vascular structure of lung, e.g. haemangioma, or distribution of aberrant vessels to pulmonary A-V fistula.
9. *CT scan* – Useful in diagnosis of pulmonary infarction, lung carcinoma, cavitary diseases like tuberculosis, bronchiectasis.
10. *Exploratory thoracotomy* – If investigations fail to reveal cause of bleeding and chest X-ray is normal, a diagnosis of idiopathic haemoptysis is justified. If X-ray lesion is present, exploratory thoracotomy is indicated.

MANAGEMENT

1. *Hospitalization* in ICU if massive haemoptysis. Sedation with diazepam or its equivalent. Pethidine or morphine is seldom necessary and a depression of the cough reflex is not desirable. Reassurance.
2. *Posture* – If site of bleeding is located, patient must be put in a semi-reclining dependent position (bleeding lung should be in dependent position)
3. *Fluids* – Colloids or crystalloids. *Blood transfusion* if profuse bleeding.
4. *Antitussives* – If cough exhausting or troublesome, small repeated doses of codeine or other cough suppressive.
5. *Antibiotics* – Useful in preventing secondary infection. Patients with active tuberculosis must be given antituberculous drugs if not already in use.
6. *Balloon tamponade* for 24–48 h. If there is no bleeding on deflating the balloon and for 6–8 h subsequently, balloon can be removed.
7. *Selective embolization of bronchial arteries* – Supplying the affected area in case of severe haemoptysis in patients with nonresectible lung cancer.
8. *Thoracotomy and surgical resection* – Indications – (a) Severe haemoptysis with site of bleeding in lung segment or lobe. (b) If embolization is unsuccessful or cannot be performed. (c) Patient continues to be hemodynamically unstable, but has good pulmonary function.
9. *Laser therapy* as palliative measure for massive haemoptysis in case of non-resectable lung cancer.

4. INFLAMMATION OF THE BRONCHIAL TREE

RESPIRATORY DEFENCE MECHANISMS

A series of immune and non-immune mechanisms working differently and at different levels, keep normal lung a bacteria free zone. However, there are various ways by which various microorganism reach lungs (Table 11).

ACUTE BRONCHITIS

Acute infection of mucous membrane of trachea and bronchi produced by viruses, bacteria or external irritants.

Causes

Precipitating causes– (i) *Infection* – Either bacterial or viral, or descending infection from nasal sinuses or throat. (ii) *Complicating other diseases* – e.g. measles, whooping cough. (iii) *Physical and chemical irritants* – Inhaled dust, steam, gases like SO_2, ether. (iv) *Allergic bronchitis* – following inhalation of pollens or organic dusts.

Symptoms

1. *Toxaemic*– Malaise, fever, palpitation, sweating, etc.
2. *Irritative* – Cough with expectoration, at first scanty viscid sputum, later more copious and mucopurulent; substernal pain or raw sensation under the sternum.
3. *Obstructive* – Choked up feeling, paroxysms of dyspnoea particularly following spells of coughing relieved with expectoration.

Signs

In early stages few abnormal signs apart from occasional rhonchi. After 2 or 3 days diffuse, bilateral rhonchi, often with rales at the bases, prolonged expiration and an expiratory wheeze.

Treatment

Appropriate antibiotic therapy, e.g. amoxicillin, cephalosporin or clarithromycin. Bronchodilators in patients with chronic airflow limitation.

CHRONIC BRONCHITIS

A clinical disorder characterised by productive cough due to excessive mucus secretion in the bronchial tree not caused by local bronchopulmonary disease, on most of the days for at least 3 months of the year for at least two consecutive years. Chronic simple bronchitis is characterised by mucoid sputum production, chronic mucopurulent bronchitis by persistent or recurrent purulent sputum production in absence of bronchiectasis and chronic asthmatic bronchitis in patients who experience severe dyspnoea and wheezing during acute respiratory infections or following inhaled irritants.

Causes

1. *Infection* – (a) Result of acute bronchitis. (b) Infective focus in upper respiratory tract, the nasal sinuses or tonsils. (c) Infective focus in lungs, e.g. bronchiectasis, fibrosis, or tuberculosis.
2. *Smoking* – particularly of cigarettes.
3. *Air pollution* – due to industrial fumes and dust.
4. *General illness* – which favour infections, e.g. obesity, alcoholism, and chronic kidney disease.

Symptoms

1. *Cough* – Constant paroxysmal, worse in winter or on exposure to cold winds or sudden change of temperature.
2. *Expectoration* – Variable, may be little, thin and mucoid or thick or frothy, mucoid and sticky. May become mucopurulent during attacks of acute bronchitis in winter.
3. *Dyspnoea* – In advanced cases, breathing becomes quick and wheezing present even at rest.
4. *Fever* – Absent except in acute exacerbation.
5. *Haemoptysis* – Usually in the form of streaks of blood.

Signs

(a) *Build* – usually short and stocky. (b) *Cyanosis* – rarely with clubbing. (c) *Signs of airway obstruction* – Prolonged expiration, pursing of lips during expiration, contraction of expiratory muscles of respiration, fixation of scapulae by clamping the arms at the bedside, indrawing of supraclavicular fossae and intercostal spaces during inspiration, and jugular venous distension during expiration due to excessive swings of intrathoracic pressure. *Widespread wheezes* of variable pitch usually most marked in expiration. Crackles at lung bases in patients with excessive bronchial secretions. Both wheezing and crackles may be altered in character by coughing.

Investigations

1. *Ventilatory indices* – Reduced PEF and VC.
2. *Chest radiography* may be normal. Infected episodes may produce patchy shadows of irregular distribution due to pneumonic consolidation and small linear fibrotic scarring may result.

Management: Principles

1. TO REMOVE THE CAUSE IF POSSIBLE – Air pollution, smoking. Elimination of aerosol sprays such as deodorants, insecticides and hair sprays. Other preventive measures include early vaccination against common influenza virus strains. Pneumococcal polysaccharide vaccine should be given only once because of danger of immunologic reactions following repeated vaccination.
2. TO PREVENT ACUTE EXACERBATIONS – By avoiding overheated rooms, damp and foggy places, stuffy clothing, overfeeding, smoking and too much alcohol. Long term treatment with tetracycline group of drugs often produces striking improvement in patients who have a purulent sputum.
3. TO TRY AND ARREST THE PROGRESS OF THE CHRONIC DISEASE BY:
   a. *Increasing patient's power of resistance* – By giving to debilitated persons abundant butter, milk or cream, cheese and other fatty articles of diet. Weight reducing measures if obesity.
   b. *Physical methods* – Regular exercises in fresh air and within limits of tolerance. Encouraging deep breathing and efficient clearance, coughing should follow a full inspiration. If economic condition permits, winter should be spent at warm resorts.
4. TO GIVE THE PATIENT AS MUCH COMFORT AS POSSIBLE – (a) *Antitussives* – such as linctus codeine if dry cough. (b) *Mucolytics* and inhalation of medicated steam. (c) *Expectorants* – (i) Ammonium salts, bromhexine or ambroxol in mixture form. (ii) Hot alkaline drink – compound sodium chloride mixture 15 ml sipped in a cup of hot water first thing in the morning. This should be followed after 15 minutes by a systematic attempt to cough the bronchi clear of accumulated secretions. (d) *Bronchodilators* – Orciprenaline sulphate or ipratropium bromide as aerosol, or Salbutamol 2–4 mg or Terbutaline 2.5–5 mg t.d.s. by mouth or 0.5% by inhaler, or theophylline orally. (e)*Antibiotics* – Clarithromycin or Co-amoxiclav for 7–14 days, a good index of response being clearing of infected sputum. Long-term chemotherapy is not indicated and

Table 12: Conditions associated with bronchiectasis

Impaired host defence
Impaired humoral or cell immunity
- Infantile X-linked agammaglobulinaemia
- Variable immunodeficiency

Immunoglobulin deficiency (primary and secondary)
- Complement deficiency
- Phagocyte defects
- Chronic granulomatous disease
- Chediak-Higashi syndrome
- Leucocyte adherence deficiency
- Ataxia telangiectasia
- Acute or chronic leukaemia (with or without IgM deficiency)

HIV-associated
Lung transplantation
Inflammatory bowel disease
- Hyperimmune states
- Allergic bronchopulmonary aspergillosis

Mucociliary clearance defects
- Immotile cilia
- Young's syndrome

(Sinopulmonary infections and obstructive azospermia)
- Immotile cilia syndrome
- Cystic fibrosis
- Kartagener's syndrome
  (Situs inversus, sinusitis, bronchiectasis)
- Chandra-Khetarpal syndrome
  (Levocardia, sinusitis, bronchiectasis)

Localized bronchial obstruction
- Inhalation of foreign body
- Benign tumour
- External compression (e.g. tuberculous lymphnodes)

Following infections
- Tuberculosis
- Measles pneumonia
- Whooping cough
- Adenoviruses 3,7,21
- Mycoplasma pneumonia
- Pneumococcal pneumonia

Lung inflammation
- Gastric aspiration
- Inflammatory bowel disease
- Toxic gas inhalation (e.g. ammonia)
- IV heroin
- Rheumatoid arthritis
- Systemic vasculitis
- Riley-Day syndrome

Miscellaneous
- Diffuse pulmonary fibrosis
- Congenital cartilage deficiency
- a_1-antitrypsin deficiency
- Yellow nail syndrome
- Primary lymphoedema
- Treated lymphoreticular malignancy
- Previous open heart surgery
- Congenital pulmonary sequestration
- Marfan's syndrome
- Ehlers-Danlos syndrome
- Post-irradiation

antibiotics should be started by the patient as soon as acute exacerbation occurs. (f) *Corticosteroids* – may be given during bad spells with an antibiotic control of co-existing infection, or if patient is severely disabled. (g) *Postural drainage* – In the patient who has a copious purulent sputum.

BRONCHIECTASIS

Bronchiectasis is a destructive lung disease characterized by chronic (permanent/irreversible) dilatation of the bronchi associated with persistent though variable inflammatory process in the lungs. These changes may involve any area but are predominantly found in the lung bases and can be divided into localized and diffuse forms. It may be associated with varied conditions listed in Table 12.

Pathology

The diagnostic feature of bronchiectasis is dilated bronchi. The Reid classification differentiates between pathological and radiological appearances of bronchiectasis.

Cylindrical bronchiectasis – Bronchial dilatation is mild and the bronchi retain their regular relatively straight outline.

Varicose bronchiectasis – Bronchial dilatation is greater and local constrictions are present, giving the airway an irregular appearance.

Saccular/cystic bronchiectasis is the most severe form and is characterized by large areas of distal 'grape-like' bronchial dilatation and loss of bronchial subdivision.

Atelectatic bronchiectasis is a localized form related to proximal bronchial distortion or occlusion.

Clinical Features

Symptoms – Clinical Types

1. *Bronchitic* – Attacks of recurrent bronchitis, more common in winter. Clubbing of fingers diagnostic.
2. *Haemorrhagic* (bronchiectasis sicca) – Recurrent haemoptysis with good health in-between, or attacks of bronchitis.
3. *Suppurative* – Chronic cough, copious purulent expectoration, general toxaemia, clubbing of fingers varying from slight parrot beak curvature of finger nails to bulbous drum stick enlargement (pulmonary osteoarthropathy). During exacerbations, dyspnoea and wheezing occur in 75% of patients and pleuritic chest pain in 50%. Pleuritic chest pain is caused by distended peripheral airways and inflammation adjacent to the visceral pleura. Pyrexia is rare during exacerbations; if it is present, pneumonia should be excluded.

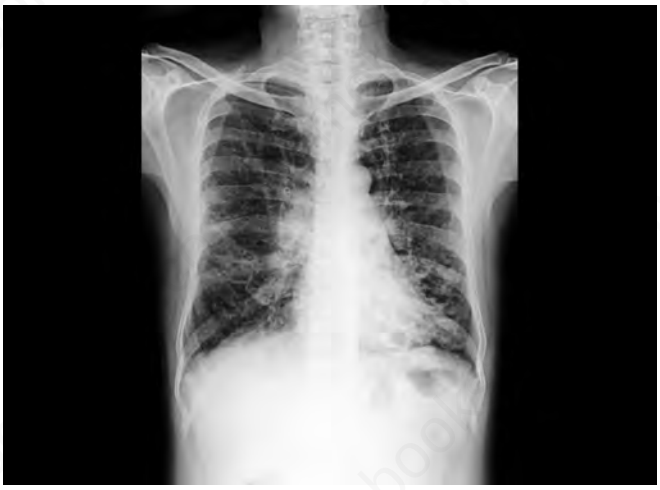


Fig. 7: X-ray chest showing streaky shadows and multiple cystic lesions with air fluid levels suggestive of bronchiectasis

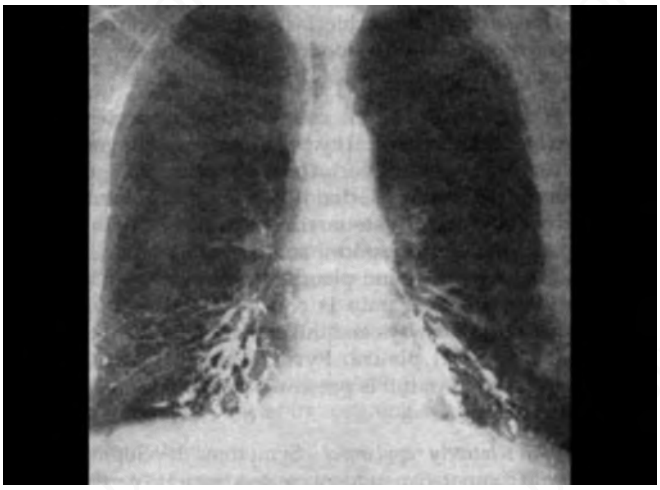


Fig. 8: Bilateral cystic bronchiectasis

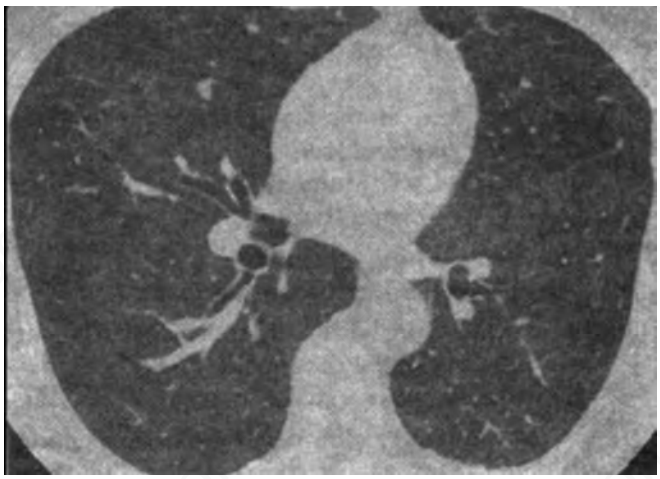


Fig. 9: High resolution CT scan of the lung showing dilated lower lobe bronchi with bronchial wall thickening and prominent adjacent pulmonary arteries

4. *With relatively rapid onset* – Symptoms developing with comparative suddenness, as a sequel to partial bronchial obstruction by a foreign body or after anaesthesia. In early stages paroxysmal cough with occasional offensive sputum which may be provoked by change of position. Later large amounts of foetid sputum.

Signs

Mostly limited to auscultation and depend on the size of the affected bronchi, patency of the airways and viscosity of secretions. There may be signs of (a) bronchitis, or (b) fibrosis, or (c) consolidation, or (d) collapse, or (e) of cavitation.

Early stages – Fine crackles or sticky rhonchi and slight alteration in character of breath sounds.

Late stages – Bronchial breathing, coarse crepts and perhaps signs of a cavity. Changing character of physical signs after a long bout of cough when air entry may become louder and bronchial in character or from day to day. Sharp metallic or "leathery" rales characteristic. Recurrent pneumonia in the same area of the lung is classically associated with bronchiectasis.

Investigations

1. SPUTUM – To exclude diagnosis of underlying pulmonary tuberculosis.

   Culture and sensitivity of infecting organism as a guide to chemotherapy.

2. RADIOLOGY:

Sinus radiographs – for chronic sinusitis.

Chest radiography – for changes suggestive or associated with the diagnosis.

- Collapse (segmental or lobar)
- Crowding of pulmonary vessels, indicating area of damage or consolidation that may become infected.
- 'Tramline shadows' suggesting bronchial wall oedema.
- Cystic lesions suggesting saccular bronchiectasis **(Fig. 7) and (Fig. 8).**
- Evidence of previous tuberculosis.
- Evidence of previous heart surgery.

3. HRCT (Fig. 9) – High-resolution CT has replaced bronchography and is the preferred investigation. CT findings include the following:
   - The 'signet ring' sign (end-on dilated bronchi that are larger than the accompanying pulmonary artery) is seen in all form of bronchiectasis

Table 13: Complications of bronchiectasis
Pulmonary – recurrent pneumonia, lung abscess, haemoptysis
Pleural – pleurisy, pleural effusion or empyema
Corpulmonale
Cerebral abscess
Amyloidosis
Seronegative arthropathy

- Tramlines (non-tapering bronchi) are seen in cylindrical bronchiectasis
- Varicose bronchiectasis has a beaded (tree-in-bud) appearance
- 'Cysts' with air-fluid levels in dilated bronchi characteristic of cystic bronchiectasis

SPIRAL CT may aid diagnosis by reducing motion artefact and identifying subtle bronchiectatic changes.

4. SPECIAL INVESTIGATIONS: may indicate the cause of bronchiectasis in some patients.

- *Immunoglobulins* – Most patients with bronchiectasis have raised plasma concentrations of immunoglobulins (especially IgA).
- *Aspergillus precipitins* – Recurrent mucus plugging of major airways and development of proximal bronchiectasis occurs in allergic bronchopulmonary aspergillosis.
- *Barium studies* – For gastrooesophageal reflux, since association of basal bronchiectasis is well recognised.
- α_1*-antitrypsin deficiency* is associated with premature pulmonary emphysema though rarely in association with bronchiectasis.
- *Detection of cystic fibrosis* – By sweat test and/or genetic analysis.

Complications

Complications of bronchiectasis are listed in Table 13.

Differential diagnosis – See differential diagnosis of lung abscess.

Management

Medical

1. **Postural drainage**– Since bronchiectasis usually affects the lower lobes the prone position with the head tilted downwards is the most useful. Deep breathing or coughing, assisted by percussion of the affected part (clapping) helps to dislodge the secretions. It should be carried out at least twice daily for 15–20 minutes at a time. Expectoration is facilitated by cough mixtures, or better inhalation of nebulized bronchodilator isoproterenol followed by inhalation of nebulized water or steam, followed by postural drainage. This should be done on arising in the morning since the patient with bronchiectasis tends to pool secretions during the night.
2. **Antibiotic therapy** – Antibiotics can delay progression in patients with cystic fibrosis. Antibiotics penetration into the bronchial mucosa and secretions is impaired and the dose needs to be higher and duration longer. *H. influenzae, H. parainfluenzae, Str. pneumonia* and *Moraxella catarrhalis* are the most common organisms in exacerbations, β-lactam antibiotics (e.g. amoxicillin 500 mg t.d.s. for 10–14 days) remain the first line therapy. Alternatives include quinolones and macrolides.

Chronic colonization with *Ps. aeruginosa* is common in severe disease. Choice of antibiotic is guided by sensitivities, but oral quinolones (e.g. ciprofloxacin 500 mg b.d. for 2 weeks) is the first time therapy. Development of resistance is common, and iv antibiotics e.g. ceftadizime 2 g t.d.s. for 14 days, gentamicin (in accordance with plasma levels), and piperacillin 4.5 g t.d.s. for 14 days, are required.

Nebulized antibiotics allow maximal concentrations of antibiotics in the airways with reduced systemic effects. Amoxicillin 500 mg b.d., gentamicin 80 mg b.d., and tobramycin solution for inhalation 300 mg b.d. can be used.

Acute exacerbations – Hospitalization in all severely ill patients, when chest pain limits coughing and sputum clearance (this increases risk of pneumonia) and iv antibiotics are required.

Prophylactic therapy – One guideline for therapy is when there are exacerbations every 2 months that prevent participation in normal activities of 2 weeks or more during the exacerbation. Continuous therapy is considered in patients who persistently expectorate purulent sputum. Aggressive treatment is warranted because persistent infection causes tissue destruction.

Bilateral lung transplantation has been used when respiratory failure develops despite optimal medical management.

3. **Intravenous immunoglobulin** replacement is thought to be effective in panhypogammaglobulinemia, but is given only to patients with established, widespread lung damage.
4. **α-antitrypsin replacement therapy** by inhaled route has the potential to neutralize damaging processes that are released as part of the airways inflammatory response.
5. **General supportive treatment** – (a) Adequate nutrition. (b) Eradication of chronic nocturnal post-nasal discharge and treatment of sinusitis. (c) Avoidance of smoking. (d) Adequate hydration.

Table 14: Indications for surgical resection

• Bronchiectasis confined to one segment or lobe of the lung causing recurrent or persistent symptoms
• Uncontrollable haemoptysis (Excision or bronchial artery embolization)
• Removal of overwhelming viscous secretions, mucous impaction or plugs
• Removal of multi-drug resistant *M. tuberculosis* or *M. avium* complex (MAC)
• Occasionally for chronic fungal superinfection, e.g. aspergilloma.

Table 16: Type of asthma

Symptoms of asthma	*Severe persistent*	*Moderate persistent*	*Mild persistent*	*Intermittent (episodic)*
Woken at night Bronchodilator (inhaled or oral) Seeks attention for acute symptoms PEF (% recent best)	>2 x / week >4 x /day Monthly <60	1-2 x /week 2-4 x /day 2-3/month 60-70	Rare <2 x /day Rarely 70-80	None With attacks For attacks >80

Surgical

Indications for surgical resection are given in Table 14.

Primary Ciliary Dyskinesia

Generalized impairment of pulmonary defence occurs with immunoglobulin deficiency, primary ciliary disorders, or cystic fibrosis.

Primary cystic dyskinesia is inherited as an autosomal recessive disorder. Numerous defects are included under this subject, such as structural abnormalities of dynes arms, radial spokes and microtubules. The cilia become dyskinetic, with diminution in their coordinated propulsion, and impaired bacterial clearance. The clinical effects include recurrent, both upper and lower respiratory tract infections such as sinusitis, otitis media and bronchiectasis, left-right body asymmetry. Because normal sperm motility also depends upon proper ciliary function males are generally infertile.

Kartagener's syndrome is one of the subgroups of primary ciliary dysfunction in which there is bronchiectasis, sinusitis and situs inversus.

Young's syndrome is characterised by recurrent sinus and pulmonary infections and obstructive azospermia. The ultrastructure of the cilia does not show the defect that are characteristic of ciliary dyskinesia (e.g. lack of dynein arms and transposition of microtubules) but show non-specific effects secondary to infection.

Table 15: Comparative features of extrinsic and intrinsic asthma

Extrinsic asthma	*Intrinsic asthma*
Young patient – child or teenager History of eczema in childhood Family history of asthma, eczema or hay fever Attacks related to specific antigens Intermittent attacks Attacks are acute but usually self-limiting Not aspirin-sensitive, occasional polyps	Adult patient over 35 or more No history of eczema in childhood Negative family history Attacks related to infection, exercise, etc Often persistent asthma Attacks more fulminant and severe Aspirin-sensitive, nasal polyps
Investigations	
Skin test with allergen extracts usually +ve Inhalation provocation test with allergens positive; negative or non-specific reactions to solvents IgE frequently raised	Skin test usually negative Normal or low IgE
Response to treatment	
Good response to beta-agonists and sodium cromoglycate	Poor response to beta-agonists, variable response to cromoglycate
Prognosis favourable	**Prognosis poor**

5. BRONCHIAL ASTHMA

Asthma is a syndrome of variable airflow obstruction. It is characterized pathologically by bronchial inflammation with prominent eosinophil infiltration, physiologically by bronchial hyper-reactivity, and clinically by variable cough, chest tightness and wheeze.

Atopy is the principal associate of asthma in individuals aged 5–30 years. It is a state of disordered immunity in which predominant T-helper lymphocyte type 2 (TH2) immune mechanisms drive production of IgE on exposure to common environmental antigens or allergens.

CLASSIFICATION

1. *Extrinsic asthma* – applies to those who produce excessive IgE in response to allergens *(atopic)*.
2. *Intrinsic asthma* – refers to those cases in whom excessive IgE production cannot be demonstrated *(non-atopic)* (Table 15).
3. *Mixed forms*

Asthma is classified on basis of symptomatology as given in Table 16.

Table 17: Triggers of asthma
Night or early morning
Exercise (especially running)
Cold air, fog
Viral respiratory tract infection
Allergens (e.g. house dust, mite, cat fur)
Nonspecific irritants (e.g. cigarette smoke, perfumes, paints)
Drugs (e.g. β-blockers, aspirin, NSAIDs)
Emotion or stress
Occupational exposure

INDUCERS AND TRIGGERS OF ASTHMA

Inducers of asthma – After birth, several factors interact to result in the clinical manifestations of asthma. Factors called inducers actually 'switch on' the asthma following which symptoms may be present for weeks, months or years.

1. **Infections** – Recurrent bouts of significant airflow limitation in constitutionally small airways may result from viral infections. The syndrome often remits as the child gets older.
2. **Cigarette smoke** – If parents smoke during the first two years of their child's life, the child is likely to develop asthma.
3. **Allergens** – The influence of both genetic and environmental factors is important and asthma is a complex response to a variety of stimuli, making it difficult to identify specific factors. (a) *Aero-allergens (inhalants)* – Such as house dust, mite allergens, tree pollens, feathers, paint, smoke, animal dander, moulds. (b) *Ingestants* – Milk, eggs, nuts, chocolates, fish, shell-fish, strawberries, etc.
4. **Induced by gastro-oesophageal reflux**
5. **Cough variant asthma. Cough predominant symptoms**

TRIGGERS OF ASTHMA

See Table 17 for triggers of asthma.

Asthmatic attack

1. *Premonitory symptoms* "asthmatic aura" – Sometimes sneezing, flatulence and drowsiness, or restlessness and irritability. Dry irritant cough may precede or accompany attacks of wheezy breathlessness.
2. *Paroxysm* – Usually sudden in middle of night. Sense of oppression in chest going into respiratory distress. Patient sits up and leans forward fighting for breath, or runs to window to relieve sense of suffocation. Anxiety, cyanosis, perspiration and cold extremities. Wheezing may be heard at a distance. On auscultation – inspiration short and high pitched, expiration prolonged, plenty of wheeze. Crackles may be heard at the bases towards the end of an attack. However, in very severe airways obstruction airflow may be so reduced that the chest is almost silent. Tachycardia especially in children.
3. *Termination* – Spontaneously or as a result of therapy. As bronchial spasm gets less, patient is able to cough a little and may bring out viscid muco-fibrin.
4. *Duration of attack* – Varies from few minutes to several hours. Sometimes paroxysms are continuous – "status asthmaticus".

Objective assessment– of variable airflow obstruction is essential for diagnosis of asthma and to determine its severity.

Home peak flow monitoring is the repeated measurement of peak flow, before and after inhaled β-agonist, at different times of day and night (if symptomatic).

Bronchodilator responsiveness is determined by measuring FEV_1 or peak flow before and after administration of bronchodilator. Diagnosis of asthma is confirmed if FEV_1 or peak flow improves > 15%.

Response to corticosteroid therapy – In some patients with relatively fixed airflow obstruction, improvement in lung function following a trial of oral or inhaled corticosteroid may be useful in confirming the diagnosis.

INVESTIGATIONS

1. *Chest radiograph* may be normal, or show signs of segmental or lobar collapse.
2. *Full blood count* – Eosinophilia.
3. Sputum – Eosinophils, Charcot-Leyden crystals and at times Curschmann's spirals may appear purulent (due to eosinophilic leucocytes) in absence of infection).
4. *Skin tests* – may confirm allergens suggested by history.
5. Lung function test – Spirometry shows reduction in FEV_1, FEV_1/FVC ratio and peak expiratory flow (PEF). Reversibility, which is one of characteristic feature of asthma, is shown by >12% or 200 ml increase in FEV_1 15 minutes after inhaled short acting β_2 agonist or 2–4 weeks trial of oral corticosteroids.
6. *Provocation (challenge) tests* – Exercise challenge tests useful in young adults and can be used to confirm diagnosis of asthma, since fall in FEV_1 or PEFR occurs after 5–7 minutes of vigorous exercise in most patients with asthma.
7. *IgE and IgE specific test* – Elevation of total serum IgE supports diagnosis of atopy, and measurement of fractions of IgE specific to one allergen, radioallergosorbent test (RAST) can be useful in some patients in whom a specific allergy is suspected.

Table 18: Differences between COPD and asthma

	COPD	*Asthma*
History		
Age at onset	Usually in adulthood	Usually in childhood
Allergy or asthma in patient's family	No	Yes
Cough and sputum	Over many years	Often recent
Dyspnoea	Usually progressive	More often paroxysmal
Variable breathlessness	Slight	Much
Attacks of breathlessness at rest	Uncommon	Common
Cough at night	Wakes then coughs	Awakens coughing
Investigations		
Improvement in PEF after bronchodilator i.e. reversible obstruction	Little or none	Usually
Daily variations in PEF		
Treatment	Little	'Morning dip' plus day to day
Effect of oral corticosteroids	Negligible	Improvement

DIFFERENTIAL DIAGNOSIS

1. **Other causes of paroxysmal dyspnoea** (Refer)
2. Chronic obstructive pulmonary disease –

Table 18 gives differences between COPD and asthma.

3. Tropical eosinophilia

Table 19 gives differences between tropical eosinophilia and asthma.

4. **Obstruction in upper respiratory tract, trachea or primary bronchus** – Dyspnoea both inspiratory and expiratory usually associated with stridor. No generalized wheeze.
5. **Allergic lung disease other than asthma** – Symptoms begin suddenly 3–6 hours after exposure to antigen with dyspnoea, cough and systemic reaction consisting of pyrexia, shivering and malaise. No evidence of airway obstruction. Some of the diseases causing allergic alveolitis are – Farmer's lung, bird breeder's lung, bagassosis, weaver's cough, etc.
(Also see D.D. of pulmonary eosinophilia).
6. **Constrictive bronchiolitis** is characterised by a concentric obstruction of respiratory peribronchiolar or inflammatory exudates leading to total scarring obstruction. Chest X-ray may be normal but a CT of the lung shows circumscribed areas of mosaic pattern. The disease occurs in collagen vascular disease (e.g. Sjögren's syn.) but also following viral infections, inhalation of toxic gas, treatment with penicillamine and gold and after bone marrow transplantation.
7. **Cryptogenic organizing pneumonia** or idiopathic bronchiolitis obliterans (idiopathic BOOP) affecting both bronchioli and lung parenchyma. The bronchioles, alveolar ducts and eventually lung parenchyma are affected.

COMPLICATIONS

1. *Respiratory* – (a) From mucus plugs – (i) Atelectasis lobar or lobular. (ii) Bronchiectasis. (b) From cough – (i) Subcutaneous emphysema. (ii) Mediastinal emphysema. (iii) Spontaneous pneumothorax. (iv) Cystic degeneration of lungs. (v) Spontaneous rib fracture. (c) From infection – Recurrent bronchitis and pneumonia. (d) From uneven ventilation and pulmonary perfusion – Respiratory failure, and cor pulmonale.
2. *Cardiac:* (a) Dysrhythmias from hypoxia and stress of asthma, compounded by bronchodilator therapy with a β-agonist and theophylline. (b) Myocardial infarction rarely in acute severe asthma.

Table 19: Differences between tropical eosinophilia and asthma

	Bronchial asthma	*Tropical eosinophilia*
History		
Age	Usually starts before 3 years of age	Any age
Duration of symptoms	Long duration	Short duration
Cough and dyspnoea	Paroxysmal cough more than dyspnoea	Dyspnoea more than cough
Fever	Rare	Breathlessness particularly after bout of cough
Loss of weight	Seldom	Common
Auscultatory signs	Compatible with degree of cough and breathlessness	Fairly common Disproportion between cough and breathlessness and signs
Investigations:		
Blood	Normal WBC count. Eosinophils 8–15%	Leucocytosis, eosinophilia marked
Chest radiograph	Increased bronchial markings	Mottling may be seen
Treatment	No known cure	Diethylcarbamazine specific

Table 20: Drugs used in asthma

Drug	*Route of administration/Dose*	*Adverse effects and comments*
A. Relievers (bronchodilators)		
β-agonists		
Short-acting (SABA)	Oral 2-4 mg	Skeletal muscle tremor
Salbutamol	Sustained release 4–8 mg	Hypokalemia
	Rotacaps 200 mg	Tachycardia
	Respirator sol. 5 mg/mL	Restlessness
	IV infusion	Hypoxemia
Terbutaline	Oral 2.5–5 mg	
	Inhalation 0.25 mg/metered dose	
	Nebulising sol. 10 mg/mL	
	Injection 0.5 mg/mL	
Long-acting (LABA)		
Inhaled Salmeterol	Inhaler 25 mg/metered dose	
	Rotacaps 50 mg	
Anticholinergics		
(Muscarin receptor antagonists)		
Ipratropium	Aerosol 20–40 mg (1–2 puffs) tds.	Safe and well tolerated Can be used as alternate or in addition To β-agonist in pts. with co-existing Chronic bronchitis
Xanthine derivatives		
Aminophylline	IV 250 mg infusion	Adverse effects likely to occur if plasma concentration >110 mmol/L Vomiting, headache, cardiac arrhythmia, abdominal pain, diarrhoea, irritability and insomnia, seizures, hypokalaemia.
Theophylline	200–400 mg bd or 800 mg nocte	
Doxofylline	400 mg bd	
B. Controllers (Anti-inflammatory)		
Chromones		
(Inhibit bronchoconstriction)		
Inhaled	5 mg metered dose aerosol	Bitter taste, throat irritation, cough Steroid-sparing effect
Disodium chromoglycate		
Oral (Nedocromil sodium)	1–2 mg bd	No bronchodilator action
Corticosteroids		
Oral / parenteral		First-line therapy for persistent disease.
Prednisolone	5–60 mg/d po	*Oral therapy:* Fluid retention, increased appetite, wt. gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataracts, and psychosis.
Methyl prednisolone	60–80 mg IV bolus q6h	
Hydrocortisone	2 mg/kg bolus q4h	
Deflazacort	6–30 mg bd po	
Aerosol		*Inhaled:* (a) Local: Dysphonia, oropharyngeal candidiasis, cough.
Beclamethasone	200–400 µg bd	(b) Systemic: Adrenal suppression, growth suppression, bruising, osteoporosis, glaucoma, metabolic abnormalities (glucose, insulin, triglycerides), psychosis.
Fluticasone	250–500 µg bd	
Budesonide	200–400 µg bd metered dose inhaler or dry powder	
Antileukotrienes		
(5-lipoxygenase inhibitor)		
Zafirlukast	20 mg bd	Mild liver dysfunction.
Zileuton	600 mg tds	Useful in asthma not controlled by inhaled corticosteroids
Montelukast	10 mg Hs	

3. *Hypokalemia:* Due to high-dose corticosteroids, high dose β-agonists, respiratory alkalosis of hypocapnia.
4. *Other complications:* (a) Nausea and vomiting from theophylline. (b) Acute myopathy due to high-dose i.v. steroids. This can lead to respiratory muscle weakness and, if patient is being ventilated, difficulty in weaning from the ventilator.

MANAGEMENT OF CHRONIC ASTHMA IN ADULTS

Drug Therapy

Drugs used in asthma are listed in Table 20.

Anti-IgE Omalizumab

It is a blocking antibody that neutralizes circulating IgE without binding to cell bound IgE. It reduces exacerbation in severe asthma but high cost is main limitation.

Step-wise approach

See Table 21 for the stepwise approach to asthma management.

Table 21: Stepwise approach to asthma management

Step 1: Mild intermittent asthma
Use of inhaled short-acting β-agonist as required for symptom relief is acceptable If these are needed more than once daily, proceed to step 2, but first ensure that the patient is taking the treatment and has a good inhaler technique
Step 2: (Mild persistent) Regular preventer therapy
Add inhaled low dose corticosteroid (beclomethasone or equivalent) 200–400 µg/day (usually 400 µg/day)
Step 3: (Moderate persistent) Add-on therapy
Add long-acting β_2-agonist Assess control of asthma by following means: Good response to long-acting β_2-agonist – continue Benefit from long-acting β_2-agonist but control remains inadequate – continue and increase inhaled corticosteroid to 800 µg/day No response to long-acting β_2-agonist – stop, and increase inhaled corticosteroid to 800 µg/day. If control remains inadequate, try other therapies (e.g. leukotriene receptor antagonist, doxofylline)
Step 4: (Severe persistent) Persistent poor control
Consider trial of the following: Increase inhaled corticosteroid to 2000 µg/day Add a fourth drug (e.g. leukotriene receptor antagonist, theophylline, β_2-agonist tablet)
Step 5: (Very severe persistent) Continuous or frequent use of oral corticosteroids
Use daily corticosteroid tablet at lowest dose providing adequate control Maintain high dose inhaled corticosteroid 2000 µg/day Consider other treatments to minimize use of corticosteroid tablets

- Avoidance of provoking factors when possible
- Patient involvement and education
- Selection of best inhaler device
- Treatment stepped up as necessary to achieve control
- Treatment stepped down if control of asthma is good

Note

- Patients should start treatment at the step most appropriate to the initial severity
- A rescue course of prednisolone may be needed at any time and at any step
- Prescribe a peak flow meter and monitor response to treatment.

Stepping Down

Review treatment every 3–6 hours, if control is achieved, stepwise reduction in treatment may be possible. Reduction may begin after a short period of time in patients in whom recently started at step 4 or 5 or included oral corticosteroid. In other patients with chronic asthma, a 3–6 month period of stability must occur before a slow, stepwise reduction is undertaken.

Status asthmaticus is the condition where severe persistent asthma does not respond to therapy.

Features of acute severe life-threatening asthma

See Table 22.

Table 22: Features of acute severe life-threatening asthma

Acute severe asthma
Any of the following:
• Peak expiratory flow 33–50% best or predicted
• Respiratory rate >25 breaths/minute
• Pulse rate >110/minute
• Cannot complete sentences in one breath

Life-threatening Asthma

Any one of the following in a patient with severe asthma

- Peak expiratory flow <33% best or predicted
- O_2 sat < 92%
- Poor respiratory effort
- Hypotension
- Exhaustion
- 'Silent' chest
- Cyanosis
- Bradycardia or other arrhythmia
- Confusion, altered consciousness or coma
- PaO_2 <8 kPa
- Normal $PaCO_2$ (4.6–6.0 kPa)

Near-fatal asthma

- Raised $PaCO_2$ (>6kPa) and/or patient requires mechanical ventilation with raised inflation pressures

Arterial gas markers of a very severe attack

- Normal or high $PaCO_2$ >(5.0 kPa) 40 mm Hg
- PaO_2 < 8 kPa
- Low pH (< 7.36)

Management

Immediate

- Oxygen– at high flow rates 6-8L/minute
- Salbutamol 5 mg or terbutaline 10 mg via oxygen-driven nebulizer
- Ipratropium bromide 0.5 mg via oxygen-driven nebulizer
- Prednisolone 30–60 mg p.o. or hydrocortisone 5 mg/kg i.v. or methyl prednisolone IgM i.v.
- Chest radiograph to exclude pneumothorax
- Aminophylline 250 mg i.v. over 20 minutes (avoid if patient on oral theophylline), or if required for more than 24 hours, serum concentration must be measured (range 10–20 mg/L)
- Salbutamol 0.25 mg i.v. or terbutaline 0.25 mg i.v. over 10 minutes.

Other treatments

- Rehydration, particularly when symptoms have been present for days before admission. Correction of plasma potassium may be required because β_2-agonists and corticosteroids can cause hypokalemia.
- Tracheal intubation is required in patients with cardiac arrest, apnoea or loss of consciousness. Following intubation, use of a benzodiazepine is indicated to ensure sedation, with neuromuscular blockade to improve pulmonary compliance and ventilation.
- Avoiding exposure to provoking factors
- No smoking
- Antibiotics – if fever or purulent sputum

Monitoring asthma control. Patients can be taught to recognise changes in the severity of acute asthma by identifying key symptoms and using objective measures of airflow obstruction such as peak flow rate.

Regular inhaled corticosteroids and intermittent β-agonists for long-term treatment; systemic corticosteroids, high dose inhaled β-agonists, oxygen therapy and medical review for acute severe exacerbations.

Integration of self-assessment and self-management with written guidelines for both long-term treatment of asthma and acute severe asthma.

6. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD is defined by the Global Initiative for Obstructive Lung Disease (GOLD) as a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

RISK FACTORS FOR COPD

Table 23 enlists risk factors for the development of COPD.

Molecular Mechanisms in COPD

Two important and mutually non-exclusive mechanisms implicated are the presence of perpetual inflammation and oxidant-antioxidant imbalance leading to oxidative stress; unlike asthma the inflammatory cells in COPD do not respond to steroids. These inflammatory cells further release battery of inflammatory mediators like cytokines, chemokines and chemoattractants which perpetuate inflammation leading to an uncontrolled cascade. Proteolytic enzymes such as elastase, proteinase-3, cathepsin G and B and matrix metalloproteinases (MMP) released by neutrophils cause damage to elastic lung tissue.

A series of pathological changes have been attributed to oxidative stress such as oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, remodelling of extra cellular matrix and apoptosis, reduction in elastin collagen synthesis and fragmentation of skeletal proteins and steroid-unresponsiveness.

PATHOPHYSIOLOGY OF COPD

1. Elastin proteolysis results in reduction in elastic recoil pressure in the lungs. Also the damage to the elastin results in significant airway narrowing.
2. Fibrotic remodelling of airways results in fixed airway narrowing causing increased air resistance that does not fully revert with bronchodilators.
3. Histological feature such as emphysema which also reduces lung elastic recoil pressure which leads to reduced pressure for expiratory and physiological features such as decreased surface area of alveoli for gaseous exchange and ventilation-circulation (V/C) mismatch.
4. Lung hyperinflation or air tapping is hall mark of COPD and is the primary cause of dyspnoea, poor quality of life and disease prognosis. The barrel shaped chest in COPD is attributed to hyperinflation of the lungs.

Table 23: Risk factors for the development of COPD

1. Genes
2. Exposure to particles
– Tobacco smoke
– Indoor air pollution from heating and cooking with Biomass fuel in poorly ventilated homes (at least 25 years of exposure)
3. Occupational dusts
a. Coal mining, cement and textile mill manufacturing, automobile drivers and vehicular mechanics, chlorinated organic compounds, dyes, rubber products, grain dust and fungi in farmers, leather manufacturing, food products manufacturing, beauty care workers and welders in automotive industries.
b. Exposure to crystalline silica – Cement industry, brick manufacturing, pottery and ceramic work, silica, sand, iron and steel, gold mining and iron and steel founding.
4. Outdoor air pollution
– Reduced lung volumes
- Lung growth and development
- Previous tuberculosis
- Early childhood recurrent lower respiratory tract infections
- Poor nutrition
• Old age (physiological obstruction)
• Low socio-economic status

Systemic Inflammation in COPD

Markers of systemic inflammation such as ESR, CRP, TLC, neutrophils, ferritin and fibrinogen are increased. Consequences of systemic inflammation are – skeletal muscle wasting, cachexia, lung cancer, pulmonary hypertension, ischemic heart disease (endothelial dysfunction), CHF, osteoporosis, normocytic anemia, diabetes mellitus/metabolic syndrome.

DIAGNOSIS

- History of chronic progressive symptoms – cough and/or wheeze and/or breathlessness.
- Reduction in FEV_1, FEV_1/FVC with obstructive pattern.

Emphysema is a component of COPD characterised by abnormal permanent enlargement of the airspaces distal to the terminal bronchioles. It is caused by a combination of mechanical obstruction in the small airways from inflammation and later scarring, and loss of elastic recoil of the lungs which makes these airways more likely to collapse during expiration.

PATHOGENESIS

There is strong association between the prevalence of emphysema and the rare genetic disorder homozygous α_1-antitrypsin deficiency; this genetic abnormality results from a complex configurational change in the α_1-antitrypsin molecule that prevents release from the liver.

The pathogenesis of emphysema in non-deficient cigarette smokers is thought to involve increased elastase release into the lungs from neutrophils that migrate into the air spaces in smokers and a functional deficiency of α_1-antitrypsin. This elastase can bind to and destroy elastin, damaging alveolar walls and leading to air space enlargement characteristic of emphysema.

A senile form of emphysema may be associated in part by degenerative vascular disease. The pathological process starts in the alveolar walls in which fenestrations or holes appear due to hypertrophy of mucosal glands and increased formation of goblet cells in the bronchi.

ANATOMICAL TYPES OF EMPHYSEMA

Centriacinar or centrilobular emphysema – The respiratory bronchioles, alveolar ducts and alveoli at the centre of the acini are destroyed. This type of emphysema tends to be more extensive in the upper lobes and apex of the lower lobes. Smokers are more prone **(Figs 10 and 11)**.

Panacinar or panlobular emphysema – Here the entire acinus is destroyed. This is the predominant type of emphysema in α_1-antitrypsin deficiency, though some smokers also develop this type of emphysema. The emphysema is more extensive in the lower lobes. Large emphysematous spaces can develop later and are termed 'bullae' when they exceed 1 cm in diameter (Fig. 12).

Paraseptal or periacinar emphysema

Involves the distal acinus.

Bronchiolitis – comprising infiltration of inflammatory cells, particularly macrophages, into bronchiolar wall is one of the earliest lesions in cigarette smokers. It can produce fibrosis of the small airways in patients with COPD.

Pulmonary hypertension – In advanced COPD with persistent hypoxemia, hypoxic vasoconstriction results in pulmonary hypertension. The oedema that usually develops in COPD patients with both hypoxemia and hypercapnia results from a complex series of events producing a reduction in renal blood flow, activation of the renin-angiotensin system, and salt and water retention.

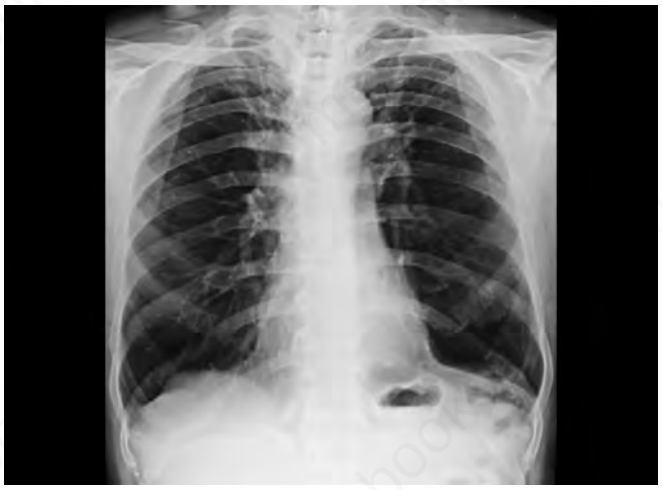


Fig. 10: Chest X-ray showing hyperinflated lungs, the diaphragm is low-lying and flat. The heart is elongated. These are features of emphysematous chest

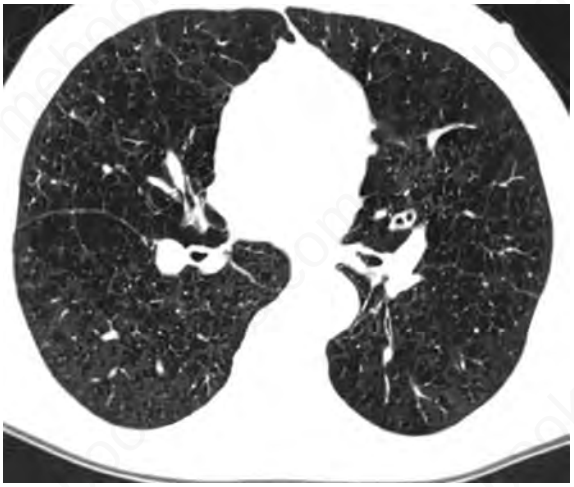


Fig. 11: Axial HRCT sections showing features of centriacinar emphysema

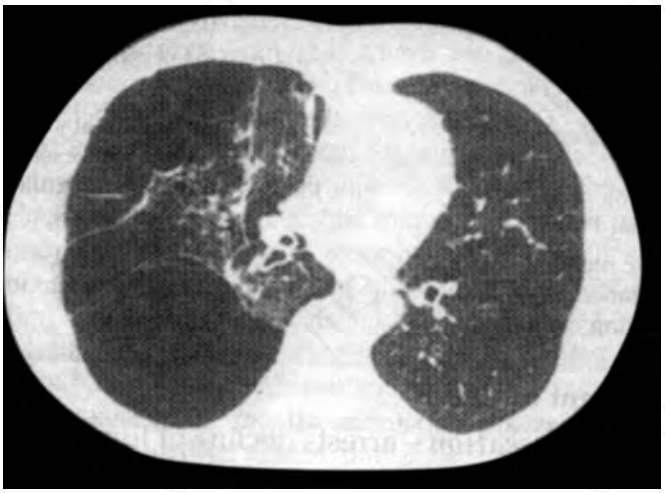


Fig. 12: Cross-sectional CT appearances of a patient with bullous emphysema. Note the relatively well-preserved lung structure in the left lung

ASSESSMENT OF SEVERITY OF COPD

GOLD criteria for assessment for severity of COPD is given in Table 24.

Blue bloater and pink puffer. These terms may reflect variation in ventilatory control. The hypersecretion of chronic bronchitis is associated with inspiratory drive in patients known as blue bloaters. Another group of patients with airways obstruction caused predominantly by emphysema retain their respiratory drive and are labelled pink puffers (Table 25).

Table 24: GOLD criteria for assessment for severity of COPD

GOLD stage	*Severity*	*Spirometry*
I	Mild	FEV_1/FVC 0.7 and FEV_1 >80% predicted
II	Moderate	FEV_1/FVC 0.7 and FEV_1 ≥50% and <80% predicted
III	Severe	FEV_1/FVC 0.7 and FEV_1 ≥30% and <50% predicted
IV	Very severe	FEV_1/FVC 0.7 and FEV_1 <30% predicted

MANAGEMENT OF COPD

1. ***Smoking cessation*** – arrests decline of lung function at all stages of disease severity.
2. ***Antibiotics for treatment of bacterial exacerbations.***
3. ***Drug therapy***

Drug therapy of COPD is given in Table 26.

4. ***Domiciliary oxygen therapy*** – Long term treatment with supplementary oxygen sufficient to raise PaO_2 to above 7.5 kPa improves survival in patients with persistent daytime hypoxemia, with or without hypercapnia.
5. ***Pulmonary rehabilitation***– comprises a coordinated programme of non-pharmacological treatment and support including exercise training, smoking withdrawal attempts and improved nutrition.

Indications for Long-Term Oxygen Therapy and Pulmonary Rehabilitation

- PaO_2 <7.5 kPa when clinically stable (i.e. at least 4–5 weeks after an exacerbation)

Table 25: Differences between blue bloater and pink puffer

	Pink puffer *(Predominant emphysema)*	**Blue bloater** *(Predominant bronchitis)*
Clinical features		
Onset	Dyspnoea and cough	Cough without dyspnoea
Build	Thin	Obese
Sputum	Scanty	Profuse, mucopurulent
Dyspnoea	Intense with purse lip breathing	Relatively mild dyspnoea
Cough	After dyspnoea starts	Before dyspnoea starts
Cardiac failure (Corpulmonale)	Rarely develop oedema or overt heart failure	Often oedematous and easily lapse into CHF
Weight loss	Marked weight loss	No marked weight loss except terminally
Bronchial infections	Less frequent	More frequent
Episodes of resp. failure	Often terminal	Repeated
Pulmonary hypertension	None or mild	Moderate to severe
Course	Unrelenting downhill	Ambulatory
Investigations:	Narrow cardiac shadow	Cardiac enlargement
Chest radiograph	Attenuated vessels	Increased bronchovascular markings
Arterial $PaCO_2$	Emphysema, Bullous changes	Raised
Elastic recoil	Normal	Normal
Resistance	Marked decrease	High
Diffusing capacity	Normal or slight increase Decreased	Normal or slight decrease

Table 26: Drug therapy of COPD

Drug	*Advantages*	*Adverse effects*
β-agonists, long acting (LABA)		
Salbutamol (and terbutaline) Metered dose inhaler 200 µg as required upto 6 times/d Dry powder inhaler: 200 µg upto 6 times/d Nebulizer: 2.5–5 mg tds or qds (PO and IV not recommended)	Rapid action Increase mucociliary Clearance	Tremor Tachycardia Can worsen hypoxia Hypokalaemia
Salmeterol 50 µg bd Formeterol 12 µg bd	Extended action No tachyphylaxis Improves health status and reduces exacerbations	Same as above Expensive
Anticholinergics		
Long-acting anticholinergics (LAMA)		
Ipratropium 40 mcg tds Tiotropium 8 mcg od As COPD severity increases to moderate type (FEVL < 80% predicted). Most patient will benefit with a combination of LABA + LAMA	Nebulised Act by blocking effect of acetylcholine on M_3 receptors	Dryness of mouth Contraindicated in narrow angle glaucoma
Methylxanthines		
Sustained release theophylline 175–300 mg bd po Doxofylline 200–400 mg bd or 800 mg at night	Oral route Anti-inflammatory effect	Slow onset of action Weak bronchodilator Drug interactions Arrhythmias and fits Nausea headache, Needs blood level measurements
Inhaled corticosteroids Beclomethasone 200–400 µg bd by metered dose inhaler or dry powder inhaler Budesonide 200–400 µg bd by metered dose inhaler or dry powder inhaler Fluticasone 250–500 µg bd by metered dose inhaler or dry powder inhaler	May improve underlying disease Lower side-effects Reduces frequency of exacerbations in patients with moderately severe disease	*Candida* infection Hoarseness Not indicated in milder disease or when no exacerbations
Mucolytics N acetyl cysteine (NAC) 600 mg bd	Reduce viscosity of sputum in the airways and help patient expectorate. Useful for recurrent exacerbations	

- $PaCO_2$>5.0 kPa when clinically stable (i.e. at least 4–5 weeks after an exacerbation)
- Previous cor pulmonale (ankle oedema/ raised JVP and abnormal blood gases as above)
- FEV_1<1.5 L and forced vital capacity >2 L
- For patients with resting hypoxemia (resting O_2 saturation <88% or <90% in patient with pulmonary hypertension or right heart failure) use of O_2 supplementation has demonstrated impact on mortality rate.
- It is also useful in patients with exertional hypoxia and nocturnal hypoxia.

6. ***Vaccine***– (a) *Influenza vaccine* given yearly 1–2 months prior to anticipated peak influenza season, because of new antigens and waning immunity from the previous year. (b) *Pneumococcal vaccine* to all COPD patients generally given only once, may be considered if last vaccination was given > 5 years previously.
7. ***Surgery*** – (a) *Bullectomy* for patients with large emphysematous bullae particularly if PaO_2 is normal and FEV_1 more than 1 litre. (b) *Lung volume reduction surgery* – Criteria include severe exercise limitation, FEV_1 < 30% predicted, dominant upper lobe emphysema on CT and normal arterial CO_2 tension. (c) Single-lung transplantation is relatively safe and effective. When marked sepsis is present, double - lung transplantation is necessary.

Management of Acute Exacerbation of COPD

Precipitating Factors

1. Infections:
   (lower resp. 50%)
   Viral: Rhinovirus spp., influenza
   Bacterial: Strep pneumonia
   H. influenzae, M. catarrhalis
   Enterobacteriaceae spp., Pseudomonas
2. Environment conditions: Sudden change in temperature and humidity, air pollution, exposure to tobacco smoke, noxious gases or irritant chemicals.
3. Host factors: Poor general health, poor nutritional status, immunocompromised pts., deficient compliance with therapy.

Symptoms

- Increased cough
- Increased breathlessness
- Fever
- Increase in cough volume and change in colour (yellow, green, blood stained)
- Chest pain
- Increased fatigue
- Increase in O_2 requirement (for pts. on long term O_2 therapy)

Investigations

- At home: Pulse oximetry
- In hospital: Chest radiograph, arterial blood gas tensions. ECG

Indications for hospitalization – 1. Unable to cope at home. 2. Severe breathlessness. 3. Cyanosis, worsening peripheral oedema, altered mental state, significant co-morbidity (heart disease, diabetes). SaO_2 <90, arterial pH <7.35, arterial PaO_2 <7 kPa.

Management

Pharmacological Treatment

A. *Bronchodilators* –

- Salbutamol 100–200 mcg inhaler and /or
- Ipratropium 20, 40 mcg with spacer or nebulizer
- If pt. is hypercapnic or acidotic, compressed air nebuliser, not O_2 (to avoid worsening of hypercapnia)

B. *Systemic corticosteroids*

- Inhaled corticosteroids by MD or hand-held nebuliser
- Prednisolone 30 mg po for 7–14 days
- IV hydrocortisone 20 mg IV up to 14 days if pt. cannot tolerate oral intake

C. *Antibiotics.* If history of purulent sputum or change in colour, consistency, volume, signs of consolidation on chest radiograph or clinical features of pneumonia. In case of sputum culture, sensitivity to antibiotics to be checked.

If pseudomonas spp. and/or other Enterobacteriaceae combination therapy, e.g. Piperacillin/tazobactam (3.375 g q4h IV) or imipenem (500 mg q6h IV) or meropenem (1 g q8h IV) plus Amikacin 7.5 mg/kg q12h or (15 mg/kg q24h IV) or Levofloxacin (500 mg daily × 10–14 days).

Theophylline IV should be used only as adjuvant if there is an inadequate response to nebulised bronchodilators. Care should be taken for the potential toxicity if pt. has been on oral theophylline.

Assisted Ventilation

1. *Non-invasive positive pressure ventilation* (NIPPV) which is a popular method of providing ventilation with a combination of continuous positive airway pressure (CPAP 4–8 cm H_2O) plus pressure support ventilation (PSV 10–15 cm H_2O). Indication for NTV - if after optimal medical therapy and oxygenation, hypercapnia, respiratory acidosis and/or excessive breathlessness persist.

Table 27: Summary of pharmacotherapy in stable COPD

Mild COPD	(a) LABA (Salmeterol alone) or LAMA (tiotropium) alone. (b) SABA (salbutamol or ipratropium + salbutamol) need-based only.
Moderate COPD	LABA + LAMA combination inhaler SABA need-based only.
Severe COPD	LABA + LAMA combination inhaler. Inhaled steroid +/- low dose theophylline.
Very severe COPD	LABA + LAMA combination inhaler. Inhaled steroid + low dose theophylline. Evaluate for home O_2 therapy. NAC 600–1200 mg /day for frequent exacerbations.

2. *Mechanical ventilation* – Indications: NPPV failure - Worsening of arterial blood gases and or pH in 1–2 hr, lack of improvement in arterial blood gases and or pH after 4 hrs, life threatening hypoxemia, tachypnoea >35 breaths/min, impaired mental status.

Steroids– Inhaled steroids reduce frequency of exacerbations in patients with severe COPD. They should be used in patients with FEVI <50% of predicted (severe disease) and/or those with 2 or more exacerbations in a year. Side-effects like oral thrush and dysphonia can be reduced by rinsing after inhaler use or use of a spacer.

Dose: Fluticasone 200–500 mcg bd. Budesonide 200–400 mcg bd.

Antibiotics – Moxifloxacin every 6 weeks for a total of 6 courses has been shown to help reduce frequency of exacerbations.

See Table 27 for summary of pharmacotherapy in stable COPD.

Oxygen therapy has been shown to reduce mortality in COPD. The flow rate of O_2 should be sufficient to maintain patient's oxygen saturation above 88% at sea level and for at least 18 hours a day. Alternatively, O_2 can be given during exercise, sleep or strenuous activity whenever the need arises.

Criteria for long-term O_2 therapy: (i) PO_2< 55 mm Hg, (ii) PO_2 55–59 mm Hg with pulmonary hypertension, corpulmonale, polycythemia, oedema from right heart failure or impaired mental state, (iii) Desaturation during sleep, exercise and high altitude.

See Table 28 for complications of oxygen therapy.

Table 28: Complications of O_2 therapy

CO_2 narcosis in patients with ventilatory failure when high concentrations of O_2 is given.
Lung complications
Pulmonary oedema
Consolidation
ARDS
Lung fibrosis
Epilepsy (idiopathic)
In neonates and premature infants
Retrolental fibroplasia and blindness
Bronchopulmonary dysplasia

7. CYSTIC FIBROSIS

Cystic fibrosis is a multisystem disorder characterised by recurrent lower respiratory tract infections, pancreatic insufficiency, high sweat chloride and male infertility.

AETIOLOGY AND PATHOGENESIS

In cystic fibrosis, the airway epithelium shows a combination of defective chloride secretion and increased sodium absorption that leads to changes in the composition of the airway surface liquid, and predisposes the lung to chronic pulmonary infections and bronchiectasis.

The *gene* for cystic fibrosis is located on the long arm of chromosome 7 and encodes the cystic fibrosis transmembrane conductance regulator (CFTR), an amino acid protein found in various cell types, including lung epithelium, submucosal glands, pancreas, liver, sweat ducts and reproductive tract. This explains the multisystem nature of cystic fibrosis.

The high sweat sodium and chloride results from defective ion absorption along the sweat ducts which are impermeable to water.

Clinical presentation – differs between neonates and older children and young adults (Table 29).

DIAGNOSIS

- **Gene mutations** – All patients must be screened for known common cystic fibrosis gene mutations.
- **Sweat test** – Both chloride and sodium sweat concentrations are > 60 mmol/L, chloride more than sodium (Sweat is collected using pilocarpine directed to the sweat glands by iontophoresis).

  Elevated sweat chloride level is pathognomonic of cystic fibrosis and levels > 70 meq/L differentiates between cystic fibrosis and other lung diseases.
- The nasal PD measurement can document CFTR dysfunction if the sweat chloride test is normal or borderline and two CF mutations are not identified.

Table 29: Differences between neonates and older children and young adults

Neonates	*Older children and young adults*
Meconium ileus Rectal prolapse Failure to thrive Recurrent bronchopulmonary infections Steatorrhoea	Chronic sinusitis Bronchiectasis Malabsorption Meconium ileus Equivalent Male infertility Cirrhosis and portal Hypertension Osteoporosis

- **Assessment of exocrine pancreas** – Faecal elastase is a useful screening test for pancreatic damage. Levels are low.
- **Lung function** – deteriorates with disease progression by about 3% per year. The picture is typically obstructive.
- **Chest radiograph** – Accentuated bronchial markings, small ring shadows, nodular shadows and more extensive confluent consolidation are characteristic findings.
- **Guthrie test** – for neonatal diagnosis. A heel prick blood test for trypsin leaking from the pancreas into the blood. Immunoreactive trypsin levels are increased by 2–3 times.

MANAGEMENT

1. *Antibiotics* – oral or IV depending on the organism. It is necessary to clear lung of secretions for which chest percussion therapy and inhalation of hypertonic saline is advocated.
2. *Recombinant human DNase* (rhDNase) –Nebulised once daily to break up long strains of DNA released by degrading leucocytes making secretions viscous. Treatment also decreases frequency of respiratory exacerbations.
3. *Anti-inflammatory agents* – to control chronic inflammation in the lungs – corticosteroids and NSAIDs.
4. *Immunization* – Patients should be given usual childhood immunizations.
5. *Nutrition* – High-calorie oral supplementation with fat-soluble vitamins A, D and E.
6. *Pancreatic enzymes* – Distal intestinal obstruction syndrome often results from inadequate pancreatic supplementation.
7. *Treatment of liver disease* – oral ursodeoxycholic acid with or without taurine.
8. *Transplantation* – Sequential single-lung or heart-lung transplantation is an option in end-stage cystic fibrosis.

8. PNEUMONIA

Pneumonia is an accumulation of secretions and inflammatory cells in the alveolar spaces of the lungs caused by infection. The infecting organism, the inflammatory response and the disturbances of gas exchange caused by alveolar involvement are responsible for the clinical manifestations.

EPIDEMIOLOGICAL CLASSIFICATION

1. Community-acquired pneumonia (CAP).
2. Nosocomial or hospital acquired.
3. Aspiration pneumonia.
4. Ventilator associated pneumonias.
5. Pneumonia in immunocompromised patients.
6. Recurrent pneumonia.
7. Unusual pneumonias.

See Table 30 for the causes of pneumonia.

Based on the anatomical part of the lung parenchyma involved.

Lobar pneumonia occurs due to acute bacterial infection of a part of a lobe or complete lobe commonly Staph. pneumoniae, Staph. aureus, β Haemolytic streptococci are responsible (Figs 13, 14 and 15).

Bronchopneumonia. Acute bacterial infection of terminal bronchioles characterized by purulent exudation which extends into surrounding alveoli through endobronchial route resulting in patchy consolidation. It is usually seen in extremes of age and in association with chronic debilitatory conditions.

Interstitial pneumonia—Patchy inflammatory changes caused by viral or mycoplasma infection, mostly confined to the interstitial tissue of the lung without alveolar exudates. Commonly mycoplasma pneumoniae, respiratory syncytial virus, Influenza virus, adenoviruses, cytomegalovirus.

MICROBIAL AETIOLOGY

1. ***Streptococcus pneumoniae*** (Pneumococcus): accounts for most cases of pneumonia and also results in more severe pneumonias.
2. ***Mycoplasma pneumoniae***– usually occurs in epidemics and in young adults. It may be associated with a persistent, non-productive cough, normal WBC, and bilateral patchy consolidation on CXR, which has led to the use of the term 'atypical pneumonia'. Certain complications (e.g. hemolytic anemia, Stevens-Johnson syndrome, neurological problems such as Guillain-Barré syndrome) can occur.

Table 30: Causes of pneumonia

1. *Bacterial* – Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, H. influenzae, Legionella spp. Also M. tuberculosis, anaerobes, Gram negative pathogens and Staph. aureus.
2. *Primary atypical:*
   a. *Viral* – Psittacosis-ornithosis group, respiratory syncytial virus, measles and influenza, cytomegalo-virus, adenoviruses, varicella, herpes zoster, lymphocytic choriomeningitis.
   b. *Rickettsial* – Coxiella burnetti (Q fever).
   c. *Mycoplasmal* – Mycoplasma pneumoniae, Stevens - Johnson syndrome.
3. *Protozoal* – Entamoeba histolytica.
4. *Yeast and fungi* – Actinomycosis, aspergillosis, nocardiosis, histoplasmosis.
5. *Chemical pneumonias:*
   a. Aspiration of vomit.
   b. Dysphagic pneumonia – pharyngeal diverticulum, achalasia cardia, hiatus hernia or oesophageal stricture.
   c. Lipoid pneumonia – Kerosene, paraffin, petroleum.
   d. Toxic gases and smokes.
6. *Radiation pneumonia.*

3. ***H. influenzae pneumonia***– occurs mainly in patients with underlying chest disease, (e.g. bronchiectasis, COPD).
4. ***Staph. aureus pneumonia*** is associated in upto 50% of cases with prior influenza virus infection. Lung abscess and empyema common. CXR – Lobar consolidation with bulging of fissure suggesting the lobe is 'stuffed' with infected material.
5. ***Tuberculosis***– should be considered if the presenting history is long, cavitation is present or response to treatment is poor.
6. ***Legionella spp.***– uncommon cause of CAP (and nosocomial pneumonia). Air conditioning systems are the most important sources of infection. Inhalation of *Legionella* by a predisposed host, (usually a smoker with chronic lung disease) leads to clinical disease which may be a mild flu-like illness (Pontiac fever) or pneumonia.
7. ***Atypical pneumonia*** refers to lower respiratory tract infections due to specific respiratory pathogens like Chlamydia psittaci (psittacosis), Francisella tularensis (tularemia), Coxiella burnetti (Q fever), Chlamydia pneumoniae, Mycoplasma pneumoniae or Legionella species.
   a. *Klebsiella pneumonia* is an important cause in some parts of the world of CAP, and the disease can be severe.
   b. *Chlamydia psittaci* is an uncommon cause of CAP. It is usually acquired from birds such as parrots, and occasionally from sheep.
   c. *C. pneumoniae* causes upper respiratory infection, but may be associated with CAP in some.
   d. *Coxiella burnetti* is a rickettsial organism which causes Q fever that may take the form of pneumonia. It is usually acquired from sheep.
8. ***Viral pneumonia*** – (a) *Influenza viruses* arethe most common viral cause of pneumonia in adults, both as primary infection and as precursor of secondary bacterial pneumonia. It has a high morbidity and mortality in elderly and in those with underlying disease. (b) *Other viruses* – Severe acute respiratory distress syndrome (SARS), Hantavirus, avian influenza and H1N1 influenza.
9. ***Other pathogens***– include melioidosis (Burkholderia pseudomallei), pneumonic plague, actinomycosis and systemic fungal infections (histoplasmosis, blastomycosis, coccidioidomycosis).

CLINICAL FEATURES

Symptoms: Onset often sudden although sometimes it follows a minor respiratory infection of a few days duration.

1. *General symptoms of infection* – Malaise, fever, rigors, and night sweats, vomiting; in the elderly confusion and disorientation.
2. *Pulmonary symptoms* – Dyspnoea, cough, and sputum which is often blood-stained or rusty and difficult to expectorate.
3. *Pleural symptoms* – Pain aggravated by cough, deep breath or movement, usually localised to site of inflammation.

SIGNS

1. *General* – Patient appears ill with tachycardia, rapid respiratory rate, high fever, flushed dry skin, herpes labialis, confusion, hypotension.
2. *Pulmonary* – (a) *Early signs* – Slight impairment of percussion note over the affected area, with weakness of breath sounds, or possibly harshness with prolonged expiration and fine crackles on deep inspiration or after cough. (b) *Signs of consolidation* – on second or

Table 31: Absence of physical signs in consolidation.
1. Deep seated pneumonia
2. Associated effusion or empyema
3. Bronchus not patent (bronchus and alveoli filled with exudate)
4. Hypostatic pneumonia at times
5. Shift of trachea

third day. (c) *Resolution* – Most signs disappear by end of second week but fine crackles and impairment of percussion note may be found longer.

At times there may not be typical signs of consolidation (Table 31). Occasionally pneumonia may be associated with jaundice (Table 32).

Table 33 lists the causes of recurrent pneumonia.

Etiological and Radiological features of pneumonia –

1. Alveolar or air space pneumonia – e.g. pneumococcal. Inflammatory exudate involves many contiguous alveoli. Segmental boundaries not preserved and bronchi remain patent. Hence nonsegmental consolidation with air bronchograms.
2. Interstitial pneumonia – e.g. mycoplasma and viral pneumonias. Inflammation mostly of interstitial septa. Hence reticular radiographic appearance.
3. Bronchopneumonia – Inflammation of terminal and respiratory bronchioles and surrounding alveoli. Hence segmental infiltrate without air bronchograms

Table 32: Causes of jaundice in pneumonia.
1. Hemolysis in mycoplasma (viral) pneumonia
2. Hepatitis in pneumococcal. Also hemolytic
3. Hepatic metastasis in lung cancer
4. Septicaemia
5. Drug-induced
6. Legionella infection.

Table 33: Causes of recurrent pneumonia.
1. LOCAL BRONCHIAL OBSTRUCTION – (i) *Intraluminal,* e.g. foreign body. (ii) *Intramural,* e.g. adenoma, carcinoma, stenosis. (iii) *Extramural,* e.g. compression by lymph nodes
2. DIFFUSE BRONCHOPULMONARY DISEASE – Bronchiectasis, cystic fibrosis, chronic bronchitis, chronic sinusitis with post-nasal drip. Recurrent pulmonary infarcts
3. NON-RESPIRATORY DISEASE – (i) Recurrent aspiration, e.g. neuromuscular and oesophageal problems, alcoholics, epileptics. (ii) Immune deficiency states.

INVESTIGATIONS

Routine Investigations

1. WBC Count – If raised points to bacterial infection.
2. Sputum gram stain and culture. Presence of > 25 WBC and 10 squamous epithelial cells per high power field suggest that the sputum is appreciate for examination. Specialised culture for *mycobacterium sp., Legionella sp.,* may be valuable in appropriate clinical circumstances. Viral cultures are not useful in initial investigation of patients with CPP.

Laboratory Diagnosis

1. *Sputum microscopy and culture* are specific tests, but their sensitivity is very low due to (a) use of antibiotics prior to the test. (b) Inappropriate sample or no sputum. (c) Atypical or viral pathogens causing pneumonia may not grow on the commonly used media.
2. *Rapid diagnostic tests (*RDTS):
   - Pneumococcal urine antigen detection test – Detects the capsular polysaccharide wall antigen common to all *S. pneumoniae* tests, with results available in 15 min. The test remains positive even after administration of antibiotics, but the sensitivity and specificity are less in children and in adults with nonbacteraemic pneumonia.
   - Legionella Urine antigen detection test: The test has high specificity and sensitivity, and rapidity (< 30 min) can be performed on patients who have taken prior antibiotic therapy. However it cannot identify Legionella infections caused by serogroups other than serogroup 1.
   - ELISA. Mycoplasma IgM ELISA assay is very useful in detecting mycoplasma pneumonia. In addition detection of cold agglutinins in blood also supports the diagnosis.
3. *Serological tests*
   - Indirect fluorescent assay detecting IgM antibodies against various atypical and viral pathogens which include Legionella pneumonia.

- *Other investigations:* Important for assessment of severity are LFTs, urea and electrolytes, and oximetry/arterial blood gases.

Patients with immunodeficiency are at risk of opportunistic pneumonias (Table 34).

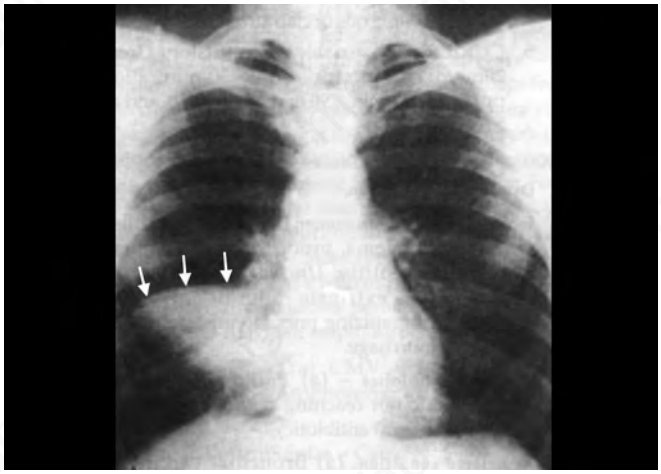


Fig. 13: Lobar pneumonia of the right middle lobe

Table 34: Immunodeficiency and risk of opportunistic pneumonias.

Primary immunodeficiency	*Secondary immunodeficiency*
B cell deficiency	HIV infection (AIDS)
(agammaglobulinaemia)	Leukaemias and lymphomas
T cell deficiency	Corticosteroid therapy
(Di George syndrome)	Cytotoxic agents
T cell and B cell deficiency	(Particularly following organ transplantation and the treatment of haematological malignancies)
(Combined immunodeficiency)	Malnutrition, general debility, uraemia, liver failure, etc.

Table 35: Radiological features and the infecting organisms.

Pneumonia	*CXR shadows*	*Occasional additional features*	*Likely organisms*
Lobar	Homogenous most of lobe or Non-segmental (patchy but confined to one lobe)	Air bronchogram Swelling or expansion of affected lobe may cavitate	Strep. pneumoniae Klebsiella pneumoniae
Bronchopneumonia	Nodular and linear opacities scattered and diffuse, when several nodules enlarge and coalesce.	Mucus plugging, inflammatory narrowing can cause volume loss, pleural effusion	Klebsiella pneumoniae, E. coli, pseudomonas Staph aureus Pneumococcus Anaerobes

FEATURES OF SEVERE PNEUMONIA

1. *Clinical:* (a) Mental confusion. (b) Respiratory rate >30 breaths/min. (c) Diastolic BP < 60 mm Hg. (d) New atrial fibrillation. (e) Multilobar involvement.
2. *Laboratory:* (a) Serum urea >7 mmol. (b) Serum albumin <35 g/L. (c) PaO_2 <8 kPa on air or oxygen. (d) WBC $<4\times10^9$/L or $>20\times10^9$/L. (e) Bacteraemia.

Radiological presentation can at times give a clue to the infecting organisms (Table 35).

Causes of Slow Resolution

- Elderly and debilitated patients.
- Infective complications – (i) Local intrathoracic – lung abscess, empyema. (ii) Metastatic – e.g. endocarditis, septic arthritis.
- Tuberculous pneumonia.
- Partial obstruction of bronchus.
- Decreased host resistance – Chronic alcoholism, cachexia, agranulocytosis, cardiac failure, immunoglobulin defects.
- Inappropriate chemotherapy.
- Superinfection due to organisms like Staph. aureus or E. coli or B. pyocyaneus.
- Confusion
- Urea >7 mmol/litre
- Respiratory rate ± 30 breaths per minute
- Blood pressure: systolic <90 mm Hg, diastolic <60 mm Hg.

DIFFERENTIAL DIAGNOSIS

a. *Pleural effusion* – Preliminary upper respiratory infection less likely in tuberculous effusion. Cough and sputum less obvious. Sputum not purulent. In early stages in pleural effusion there may be bronchial breathing. White cell count normal.

b. *Pulmonary infarction* – Sudden onset but no rapid rise of temperature or rigor as in pneumonia. Blood-stained sputum and presence of predisposing condition like obvious venous thrombosis or heart disease.

c. *Bronchiectasis* – Recurrent infection and persistently muco-purulent expectoration. Finger clubbing. Coarse basal crackles.

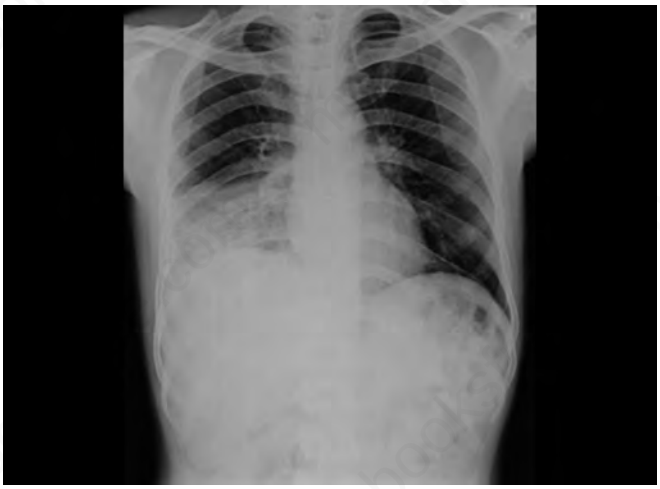


Fig. 14: X-ray chest showing right lower lobe pneumonia

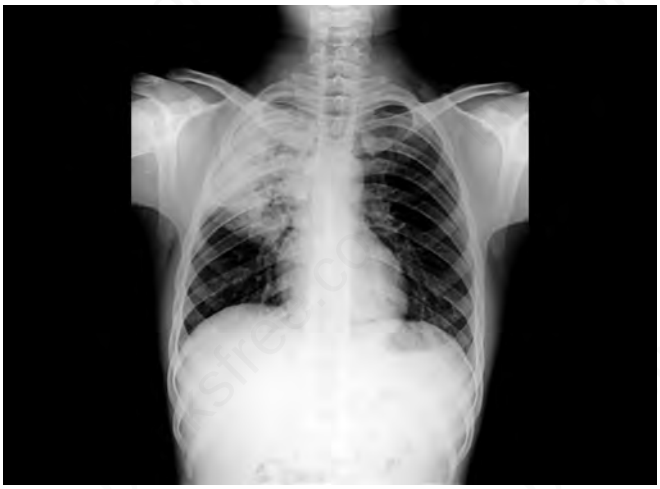


Fig. 15: X-ray chest showing right upper lobe pneumonia

d. *Atelectasis* – Detection of cause such as inhaled foreign body, or post-operative or following trauma. Displacement of mediastinum.

e. *Lung cancer* – Patient may present with pneumonia affecting the ill-drained lung beyond the growth. Superimposed hilar shadows on X-ray may give clue to underlying pathology.

f. *Exacerbation of asthma* – Patient known to have asthma, wheeze on examination.

g. *Fibrosing alveolitis* – Long history of chronic cough that produces large amount of purulent sputum.

- (h) *Subdiaphragmatic conditions* – Subphrenic abscess or pancreatitis may present as lower lobe pneumonia.

MANAGEMENT

1. *Hospitalization* – If advanced age, signs of severe illness these can be remembered as the 'CURB' severity score.
2. *Fluids* – IV in those with severe illness or vomiting.
3. *Oxygen* – If initial blood gases indicate hypoxemia (PaO_2 < 10 kPa). If oxygenation is inadequate continuous airways pressure may be sufficient to improve gas exchange, otherwise intubation and assisted ventilation.
4. *Antibiotics:*

A. For out-patients

a. For healthy and not received antibiotics in last 3 months
   i. Macrolide – azithromycin 500 mg PO OD or clarithromycin 500 mg PO BID or
   ii. Doxycycline 100 mg PO BID

b. Comorbidities or received antibiotics in last 3 months
   i. Fluroquinolones - Levofloxacin 750 mg/ Moxifloxacin 400 mg – PO qd or
   ii. β lactam agents Amoxycillin + Clavulanic acid (2 gm bid)/Ceftriaxone 1–2 gm IV qd/Cefpodoxime 200 mg bid/Cefuroxime 500 mg bid + macrolide

B. For inpatients

a. β lactam agents Inj. Amoxycillin + Clavulanic acid (2 gm bid)/Ceftriaxone 1–2 gm IV qd/Cefotaxime 1–2 gm IV + macrolide or fluroquinolone IV

b. For specific organisms
   i. Pseudomonas
      1. Antipseudomonal β lactam agents – Inj. Piperacillin and Tazobactam (4.5 gm q6h)/Inj. Cefipime (1–2 gm bid)/Inj. Imipenem (500 mg q6h)/Inj. Meropenem (1 gm tds) + Inj. Levofloxacin 750 mg qd
      2. Above Antipseudomonal β lactam agents + Aminoglycoside Inj. Amikacin (15 mg/kg qd) + Azithromycin
   ii. MRSA
      3. Need to add Inj. Linezolid 600 mg IV q12hrly or Inj. Vancomycin 15 mg/kg q12hrly

5. CURB uses 5 variables + confusion, Urea >20 mg/dL, Respiratory rate >30 min, Blood pressure (Systolic ≤90 or diastolic ≤60, and age >65 years.

Failure of Treatment

Causes of failure of treatment are given in Table 36.

PREVENTION FOR CAP

Prevention is done mainly through vaccination.

Pnumococcal vaccines are available for preve ntion.

PPV 23 is pneumococcal polysaccharide vaccine and PCV13 is protein conjugated with capsular polysaccharide. Both are known to reduce overall incidence of pneumonia in children and adults.

PCV13 is recommended for elderly and younger immunocompromised patients.

Influenza vaccines are available both inactive, given intramuscularly, and live attenuated, given intranasally,for population who are at high risk for morbidity and mortality like extremes of ages, pregnancy, suffering from chronic lung diseases.

Stopping smoking is known to reduce risk of pneumococcal infection in patients of COPD.

NOSOCOMIAL PNEUMONIA

Pulmonary infection that develops 2 days or more after hospital admission.

Causes – Etiologic organisms include Pseudomonas aeruginosa, Staph. aureus, Gram-negative enterobacteria. Also S. pneumoniae, Legionella, viruses (respiratory syncytial virus, parainfluenza and influenza A).

Diagnosis – Examination of sputum with Gram staining. Specimens obtained at bronchoscopy with protected brush catheter or bronchoalveolar lavage. Presence of new and/or progressive pulmonary infiltrates (often in lower lobes, esp. rt. lower lobe) with new onset of fever, leucocytosis and purulent sputum is often considered as clinical evidence.

Management

Mild	Co-amoxiclav 500 mg tds.
Severe	Cefuroxime 750 mg i.v. q8h + Clarithromycin 250mg q8h

Table 36: Causes of failure of treatment

1. **Overwhelming infection.**
2. **Incorrect diagnosis** – *Common*: Pulmonary embolism, pulmonary oedema, bronchogenic carcinoma, fibrosing alveolitis. *Uncommon*: Pulmonary eosinophilia, extrinsic allergic alveolitis, cryptogenic organizing pneumonitis, pulmonary alveolar hemorrhage.
3. **Incorrect antibiotics** – (a) Pathogen resistant. (b) Antibiotic not reaching pathogen (e.g. poor absorption of oral antibiotic).
4. **Associated condition—** (a) Bronchial carcinoma. (b) Immunocompromised patient.
5. **Complications—** Empyema, lung abscess, metastatic abscess, secondary nosocomial infection, pulmonary embolus.
6. Antibiotic hypersensitivity.

ASPIRATION PNEUMONIA – SEE LUNG ABSCESS PNEUMONIA IN THE IMMUNO-COMPROMISED HOST

Aetiology– Infection may be caused by almost any organism but bacterial infections with pseudomonas, Klebsiella, E. coli and S. aureus are the most common. The four most opportunistic pathogens are pneumocystis, CMV, aspergillus fumigatus and candida.

Diagnosis – (a) Invasive techniques –Percutaneous lung aspiration. (b) Bronchoscopy to obtain protected brush catheter specimens, bronchoalveolar lavage, transbronchial biopsies. (c) Chest radiograph – Other possible cause for acute lung shadowing in a patient receiving immunosuppressive therapy are – (i) Pulmonary oedema. (ii) Pulmonary hemorrhage from bleeding disorders or vasculitis. (iii) Underlying disease directly affecting the lung (e.g. tumour). (iv) Pulmonary reaction to radiotherapy or drug treatment – e.g. bleomycin or cytotoxic agents. (v) Infection. Focal radiologic shadows and mucopurulent sputum would suggest bacterial pathogens. Bilateral diffuse shadowing would be more typical of pneumocystis or cytomegalo (CMV) virus. Multiple discrete peripheral fluffy shadows perhaps with cavitation, may point to fungal or staphylococcal infection.

Management – (a) CMV – IV Ganciclovir.(b) Aspergillus – Amphotericin B. (c) Candida – Amphotericin B.

VENTILATOR-ASSOCIATED PNEUMONIA

Pneumonia is one of the common complications arising in patients on mechanical ventilation which leads to increase ICU stay, difficulty in weaning from mechanical ventilatition and thus increasing medical cost as well as mortality and morbidity.

These patients are prone for infection by multi drug resistant (MDR) pathogens which includes (1) Psudomonas aeruginosa, (2) MRSA, (3) Acinetobacter sp, (4) Enterobacteriaceae.

Following factors play role in pathogenesis for VAP:

1. Colonization of oropharynx with pathogenic mivrobes which replace normal flora due to antibiotic selection pressure, cross infection from other patients or contaminated equipments and malnutrition.
2. Aspiration of these pathogenic organisms from oropharynx.
3. Compromised host defense mechanisms

Clinical Features

New-onset fever, increased respiratory secretions, tachypnoea, tachycardia, worsening oxygenation and increased minute ventilation.

Investigations

It shows leucocytosis, new or changing infiltrates on X-ray.

Culture of organism is main step in management of VAP which allows antibiotic sensitivity testing and helps to start specific treatment. Endotracheal aspirate is used for culture. More distal in respiratory tree diagnostic sampling done, more specific results are obtained.

Management

1. Hand washing: It is known to reduce significant cross infection and transmission of MDR pathogens from ICU.
2. Head elevation: Head end should be elevated to 45^0 to reduce aspiration.
3. Heavy sedation avoided.
4. Antibiotics: Choice of antibiotic should be guided by culture and sensitivity report. Till the time culture reports are available patient should be started on broad spectrum antibiotics which should include

Antipseudomonal β lactam agents – Inj. Piperacillin and Tazobactam (4.5 gm q6h)/Inj. Cefipime (1–2 gm bid)/Inj. Imipenem (500 mg q6h)/Inj. Meropenem (1 gm tds) + Inj. Levofloxacin 750 mg qd or Aminoglycoside Inj. Amikacin (15 mg/kg qd) + Inj. Linezolid 600 mg IV q12hrly or Inj. Vancomycin 15 mg/kg q12hrly

5. Monitoring done with WBC counts, X-ray and O_2 requirement.

Unusual pneumonias – See Table 37 for Causes.

Table 37: Causes of unusual pneumonias

Bacterial
• Acute TB
• Salmonella typhi and paratyphi
• Brucellosis
• Plague
• Tularemia
• Anthrax
Viral
• SARS
• Swine influenza (H_1N_1)
• CMVS pneumonia
• Hantavirus pulmonary syndrome
Spirochaetal
• Leptospirosis
Rickettsial
• Typhus
Protozoal, yeast and fungi
• Coccidioidomycosis
• Actinomycosis
• Histoplasmosis

9. LUNG ABSCESS

Circumscribed suppurative inflammation of lung by pyogenic organisms leading to cavitation and necrosis.

CAUSES

1. *Aspiration abscess* – Aspiration of infected material – (a) From upper respiratory tract – Oral or pharyngeal sepsis, oesophageal obstruction, tracheo-oesophageal fistula, drowning. (b) Vomit. (c) Bronchiectasis. (d) Iatrogenic following use of intermittent positive pressure breathing therapy and nebulisers.
2. *Specific abscesses* – (a) Lobar pneumonia particularly Klebsiella, Staphylococcal or haemolytic streptococcal pneumonia. (b) Tuberculosis. (c) Fungal infection, e.g. actinomycosis.
3. *Bronchial obstruction or stenosis* – Benign tumours, or inspissated bronchial mucus or foreign body, mucoviscidosis.
4. *Metastatic lung abscess* – Suppurative thromboembolism involving lung parenchyma – pulmonary embolism from pelvic thrombophlebitis or right sided endocarditis, or during septicaemia and pyemia.
5. *Malignancy* – Necrosis within a large solitary nodular malignant neoplasm.
6. *Infected cysts or bullae* – Congenital or acquired.
7. *Extension from neighbouring organs* – Diaphragm, e.g. amoebic infection, vertebral column.
8. *Other* – Wegener's granulomatosis, pneumoconiosis (silicosis, coal).

Symptoms – Groups:

1. *Mild general toxaemia* – with slight fever. No symptoms referable to respiratory tract.
2. *Sudden onset* – with high fever, pleuritic chest pain, cough and later copious expectoration.
3. *Symptoms of subacute or chronic respiratory disease* – cough, foetid breath, expectoration and general toxaemia. Haemoptysis may occur, or pain due to associated pleurisy.

Signs: Depend on situation and size of abscess and surrounding infiltration.

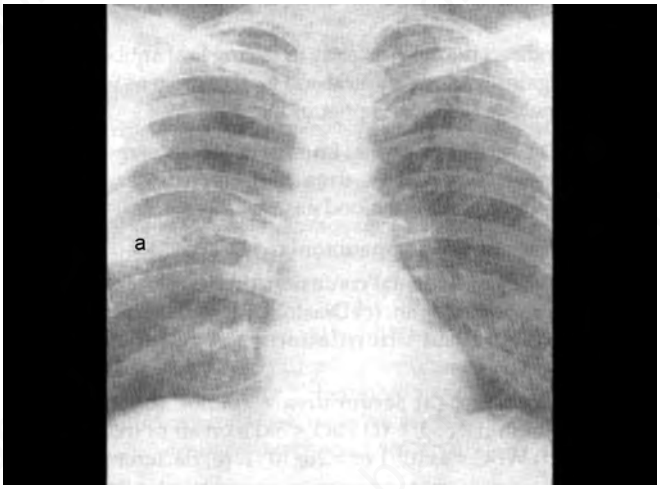


Fig. 16: Segmental involvement (a) in viral pneumonia. The consolidation lacks homogeneity

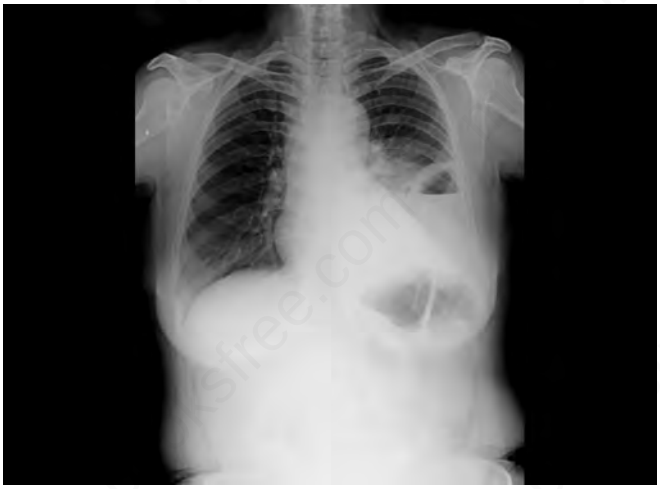


Fig. 17: X-ray chest showing a thick walled abscess cavity with air fluid level in left lower lobe

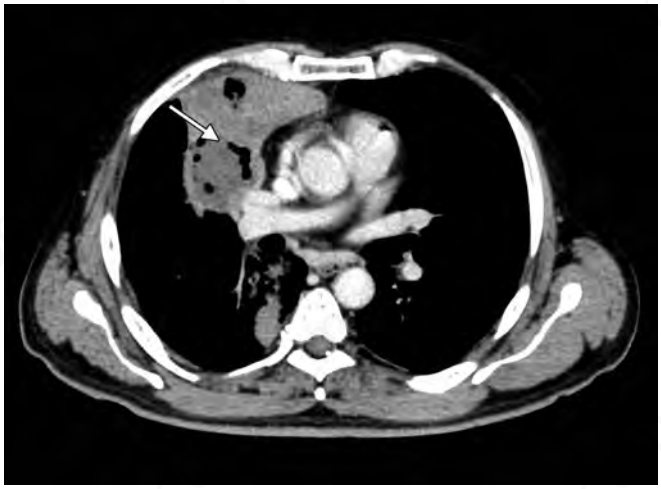


Fig. 18: CECT chest axial view showing right middle lobe atelectasis with lung abscess

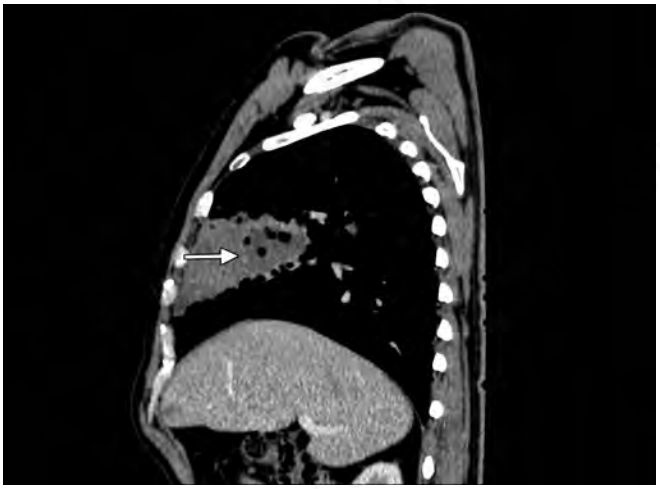


Fig. 19: CECT chest coronal view showing right middle lobe atelectasis with lung abscess

1. *In early stages* – Pleural rub, local area of dullness and weak breath sounds or signs of consolidation.
2. *After evacuation of pus* – Signs of cavitation or signs of localized consolidation with amphoric or cavernous breath sounds and crackles of the resonating variety.
3. *Signs of effusion* – may overshadow those of the lung lesion.
4. *Clubbing of fingers.*

INVESTIGATIONS

1. *Leucocyte count* – 20,000 to 30,000 cells per c.mm.
2. *Sputum* – Pus cells, organisms and necrotic lung tissue.
3. *Chest radiograph* **(Fig. 17)** – In acute phase dark shadow, later cavity with fluid level.
4. *Bronchoscopy* – to exclude foreign body or carcinoma.
5. *CT scan* **(Figs 18 and 19)**

COMPLICATIONS

- Haemoptysis.
- Extension of inflammation to other parts of lung.
- Cerebral abscess.
- Rupture into pleural cavity.

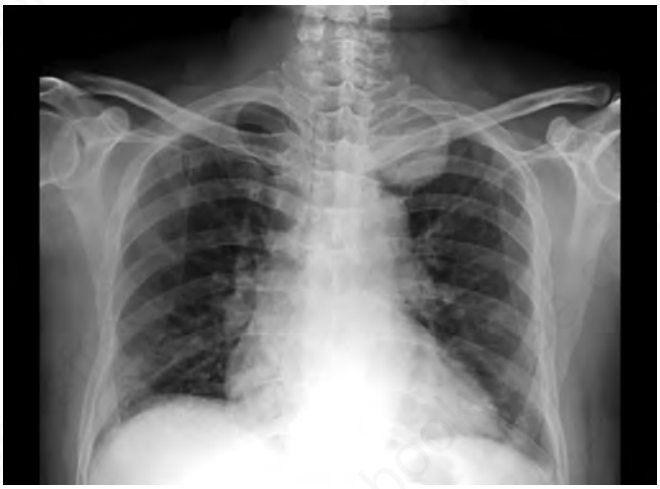


Fig. 20: X-ray chest showing a well-defined with smooth outline, rounded soft tissue density lesion in the superior mediastinum paratracheal in position, extending into left lung apex

DIFFERENTIAL DIAGNOSIS

1. *Bronchiectasis* – History of cough influenced by posture and associated with copious sputum. Leathery crackles and variable physical signs. No elastic tissue in sputum. X-ray characteristic.
2. *Cavitated bronchial carcinoma* – Elderly patient. Pain in chest, cough and dyspnoea and other pressure symptoms. May be enlarged cervical or axillary lymph nodes. Cancer cells in sputum.
3. *Purulent bronchitis* – Long history. Widespread physical signs. No elastic tissue in sputum.
4. *Caseating tuberculosis* – Signs usually apical. Rapid wasting. Positive sputum.
5. *Interlobar empyema* – Signs generally more marked in axilla or near angle of scapula. Usually few signs. Diagnosis difficult without X-ray which will show an elliptical density in line of one of the fissures in lateral film; shadow with sharply outlined borders.
6. *Infected lung cyst* – Particularly bronchogenic **(Fig. 20)** and hydatid, difficult to differentiate unless previous X-ray shows uninfected cyst or cysts in other parts of the lung. Radiologically there is a clear-cut spherical shadow with little or no surrounding pneumonitis.
7. *Pulmonary infarction* – Postoperative or antecedent cardiovascular disease. Friction rub may be heard. Sputum may be blood stained. X-ray normal or wedge-shaped consolidation.
8. *Empyema with bronchopleural fistula* – Fistula can be demonstrated by injecting 2 mL of 1% methylene blue into the empyema and examining the sputum for the dye.
9. *Pulmonary haematoma* – History of chest trauma. Sputum not purulent and little cough. Spontaneous cure.
10. *Pulmonary mycoses* – Cough, expectoration which may be offensive, dyspnoea. Fever and night sweats. Diagnosis by identification of the fungus in the sputum.
11. *Infected pulmonary bulla with fluid level* – Patient not so ill. Air-fluid level in a cavity with a thin wall.
12. *Cavitated pneumoconiosis* (Caplan's nodules) – Occupational history. Evidence of pneumoconiosis in rest of the lungs.
13. *Cystic fibrosis (mucoviscidosis)* – Symptom complex of (a) pancreatic insufficiency, (b) chronic bronchopulmonary infection and (c) high sweat sodium. Picture similar to bronchiectasis but usually increased number of infectious flare-ups, more airway obstruction, earlier and more pulmonary insufficiency and poorer nutrition due, in part to exocrine pancreatic insufficiency, (d) atopy in majority. CXR – streaky or patchy shadows with or without cavitation.

14 *Wegener's granulomatosis* – Respiratory symptoms such as cough, haemoptysis, dyspnoea. Lesions bilateral and in lower lung fields. Cavitation with thin walls may be seen with sharply outlined borders.

MANAGEMENT

1. GENERAL – (a) Rest in bed. Ambulation as soon as signs of toxicity disappear. (b) High caloric, high protein diet with additional vitamins. (c) Transfusions as indicated. (d) Deep breathing exercises to encourage drainage.
2. MECHANICAL PROCEDURES – (a) *Postural drainage* – Percussion therapy or "clapping" over the site of the abscess with the patient in the postural drainage position is often effective in dislodging and expelling secretions from the cavity. (b) *Bronchoscopy* – Suction is applied to the orifices of the bronchi leading to segments presumed to be involved in the process in hope of initiating or promoting drainage. In addition any foreign material is removed and a careful search made for a tumour. (c) *Oxygen inhalations* – when sputum is foul because it checks the anaerobic organisms (d) Head elevation – patient bed should be inclined to 45^0 from horizontal plane in cases of altered mentation, on mechanical ventilatory support. (e) Minimal sedation used to avoid aspiration.
3. CHEMOTHERAPY – The most effective antibiotic is determined by culturing the sputum and testing the causative organism against the available drugs. Penicillin is the most useful antibiotic in the common forms of lung abscess. Amoxicillin 1 g. t.d.s. p.o. + Metronidazole 400 mg t.d.s. p.o. or Co-amoxiclav 500 mg t.d.s. or Clarithromycin 250–500 mg t.d.s.

Inj. Clindamycin 600 mg three times a day till fever disappears then switched to 300 mg four times a day orally or Inj. B lactam/β lactamase inhibitor combination is used and as fever subsides switched to oral therapy.

4. BRONCHOSCOPY – may be needed to remove particulate matter or to exclude bronchial obstruction.
5. SURGICAL RESECTION – If at end of 3 weeks, there is no clinical and radiological improvement, segmental resection of lung, lobectomy or pneumonectomy. Also if localized malignancy or massive haemoptysis.

PROGNOSIS

Following factors indicate poor prognosis:

1. Age > 60 years
2. Sepsis at presentation
3. Abscess size > 6 cm
4. Aerobic growth on culture
5. Symptoms longer than 8 weeks

10. PULMONARY TUBERCULOSIS

RISK FACTORS

- *Close contact* with sputum-smear positive individual.
- *Environmental factors* that lower resistance – Malnutrition, poor and overcrowded housing, alcoholism and/ or drug addiction, heavy smoking, corticosteroid therapy.
- *Relation* to *other disease* – Not uncommon after influenza, whooping cough. More common with diabetes mellitus, cirrhosis of liver, pneumoconiosis, and following partial gastrectomy.
- *Immunosuppression* (including drugs and autoimmune deficiency syndrome).
- HIV infection/AIDS.
- Other risk factors – Kidney failure, diabetes, silicosis, family history, IV drug abuser.

Route of infection – In majority by inhalation of air-bone infected droplet nuclei derived from sputum of an adult with cavitary pulmonary tuberculosis.

CLINICAL TYPES

I. **Primary pulmonary tuberculosis** – Primary tuberculosis refers to events following invasion by tubercle bacillus infection, being commonly caused by inhalation (rarely through skin or ingestion) of the bacilli into the lungs.

Primary complex– Inhaled bacilli are deposited in the alveoli where a subpleural inflammatory lesion occurs. When they reach the regional lymph nodes, these also become infected. (Ghon primary complex) The tuberculin test becomes positive within 6 weeks of the infection. These two components of the primary complex may resolve without complications and sometimes result in local calcification (Fig. 21).

Progress – of primary complex may occur thus:

1. **Haematogenous dissemination**– about 3 months after primary infection. (a) Acute type – Miliary tuberculosis, TB meningitis. (b) Chronic type – with local manifestations in kidneys, bones, and joints.
2. **Progress of lung component**– most commonly in adolescents and young adults usually about 6 months after initial infection. The lung focus extends, cavitates and pleural involvement leads to pleural effusion.
3. **Progress of lymph node component**– It may cause pressure on trachea or main bronchi resulting in severe paroxysmal cough simulating whooping cough. There may also be dyspnoea, stridor or wheezing which may be mistaken for asthma.
4. **Bronchial involvement:**
   a. *Partial bronchial* obstruction with valve action causing obstructive emphysema or
   b. *Complete bronchial obstruction* may result in large areas of homogenous shadowing. Bronchial involvement commonly involves middle lobes and upper lobes. Aspiration of infected material causes pneumonia or collapse. Lesions may clear without sequelae but sometimes result in permanent collapse, bronchostenosis, bronchiectasis or obstructive emphysema.
   c. *Middle lobe syndrome* – Compression of a bronchus by enlarged lymph nodes can cause pulmonary collapse. The large middle lobe bronchus is particularly vulnerable and the bronchiectasis may lead to recurrent middle lobe infection.

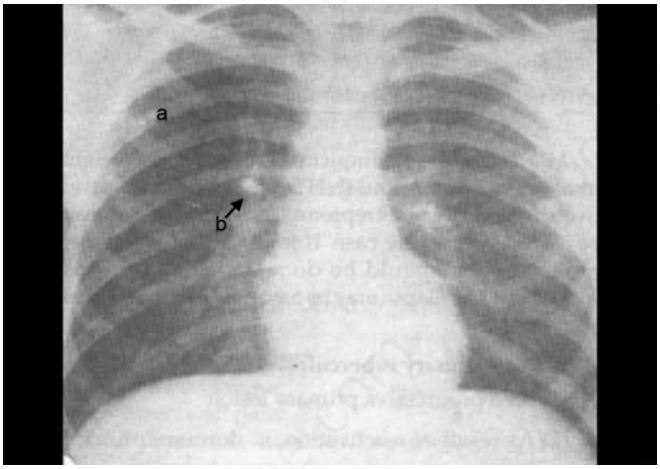


Fig. 21: Primary tuberculous infection. Calcified focus in the lung (a), calcification in the hilum (b)

Table 38: Differences between primary complex and reinfection

Reinfection	*Primary complex*
1. Absence of enlarged hilar lymph nodes.	1. Enlargement of hilar lymph nodes.
2. Usually subapical location.	2. Any part of lung.
3. Tendency to cavitation and progress.	3. Usually heals. Cavitation rare, thin walled.
4. Spread bronchogenic hence disease is localised to the lungs.	4. Spread by lymphatic route and haematogenous. Miliary spread common.
5. Healing of the lesion by fibrosis.	5. Healing of lesion mainly by calcification.

Table 38 gives differences between primary complex and reinfection.

MANAGEMENT – Rifampicin 12 mg/kg body weight (maximum 600 mg) and INH 5 mg/kg body weight in two divided doses. Streptomycin 50 mg/kg/day can be added in a severe case. If lesion is not resolving, bronchoscopy should be done and the bronchus sucked out as collapse may be associated with retained secretions.

II. **Post-primary tuberculosis** – Reactivation

1. As a progressive primary lesion.
2. As result of reactivation of dormant/primary lesion.
3. Haematogenous spread to the lungs

A. Acute pulmonary tuberculosis:

1. ***Pneumonic tuberculosis***– affects usually upper lobe, rarely whole lung. Symptoms like acute lobar pneumonia, but irregular temperature, rapid breathing, sweats, signs of cavitation. Leucopenia and failure to respond to antibiotics.

   Upper lobes are affected because TB bacillus is a strict aerobe and the upper lobes of the lungs have the highest alveolar oxygen tension.
2. ***Bronchopneumonic tuberculosis***– Abrupt onset at times following influenza, or in children measles or whooping cough, or as a sequel of haemoptysis with aspiration of tuberculous matter into bronchi. Signs of diffuse bronchitis in early stage, later areas of consolidation especially at apex. Rapid wasting. X-ray shows scattered foci throughout lungs. May be rapidly fatal.
3. ***Miliary tuberculosis*** – Types

   i. ACUTE MILIARY TB

CLINICAL FEATURES

a. *Onset* – Gradual with vague ill-health, loss of weight and fever.

b. *Fever* – irregular, wide variation between morning and evening.

c. *Hepatosplenomegaly* – in 20–30% of cases.

d. *Respiratory symptoms* – Dyspnoea and cyanosis out of proportion to signs in chest. Slight dry cough, scattered wheeze and occasional crepts.

e. *CNS* – Headache common, often severe. Signs of meningeal irritation in early stages.

f. *Cardio-vascular* – Tachycardia.

g. *Skin* – Miliary lesions of skin rarely as macules, papules or purpuric lesions.

h. *Fundus* – Choroid tubercles pathognomonic. Seen as single or multiple yellowish white spots which later become pigmented.

INVESTIGATIONS

Mantoux text – Positive in majority.

Chest radiograph – Scattered opacities throughout the lung fields – "snow storm appearance" (Fig. 22).

HRCT chest - **(Figs 23 and 24).**

Complications – 1. TB meningitis. 2. Pleural effusion or polyserositis. 3. Cervical lymphadenitis. 4. Hypokalaemia. 5. Blood dyscrasias – Anaemia with pancytopenia, at times leukaemoid reaction, purpura.

ii. CRYPTIC (OBSCURE) MILIARY TB

Occurs in elderly patients with prolonged low grade fever, hepatosplenomegaly may occur. Chest radiograph is usually normal, miliary mottling may appear months later. Tuberculin test is usually negative.

iii. ACUTE DISSEMINATED HAEMATOGENOUS TUBERCULOSIS:

- *Clinical features* – (i) Pyrexia of unknown origin lasting over few weeks, with sudden deterioration especially in immuno-compromised patients. (ii) Sputum absent or scanty. (iii) ARDS. (iv) Tachypnoea. (v) Development of dysfunction of multiple organs resembling sepsis.
- *CXR* – Miliary or scattered shadows.
- *Bronchoscopy* – AFB may be cultured from samples from bronchoalveolar lavage and caseating granulomas may be seen on histopathology of lesion obtained from transbronchial biopsy.
- *Liver cell dysfunction.*

B. Chronic pulmonary tuberculosis:

MODES OF PRESENTATION –

1. Symptom-free – Diagnosis on routine radiography.
2. Insidious – Malaise, undue fatigue, loss of weight, evening rise of temperature, and cough.
3. Persistent cough or "smoker's cough".
4. Unexplained loss of weight.
5. Pyrexia of unknown origin.

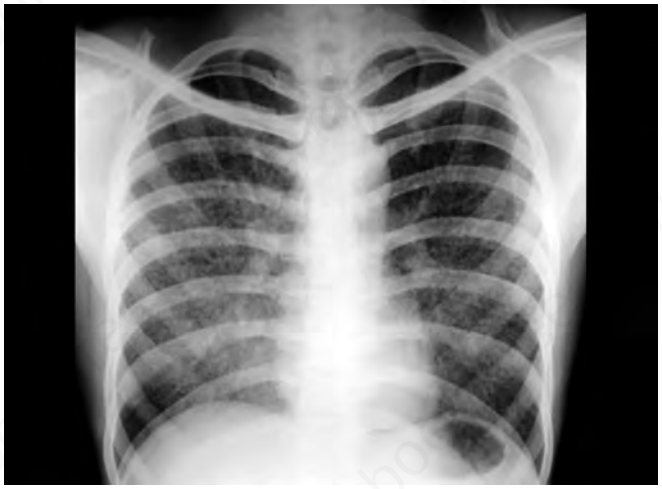


Fig. 22: X-ray chest showing miliary tuberculosis

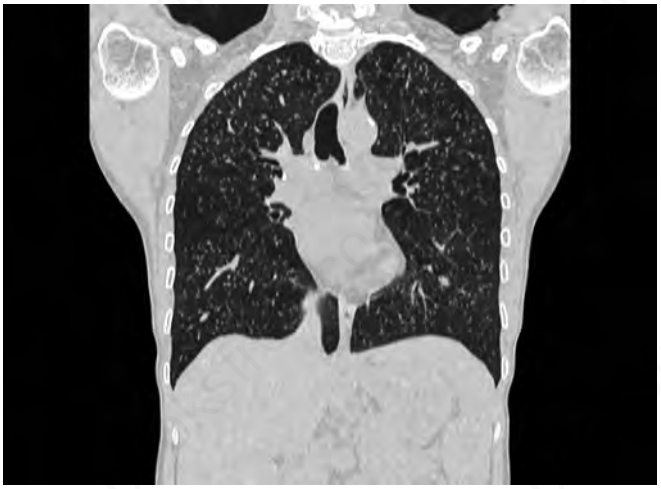


Fig. 23: HRCT chest coronal view showing miliary tuberculosis

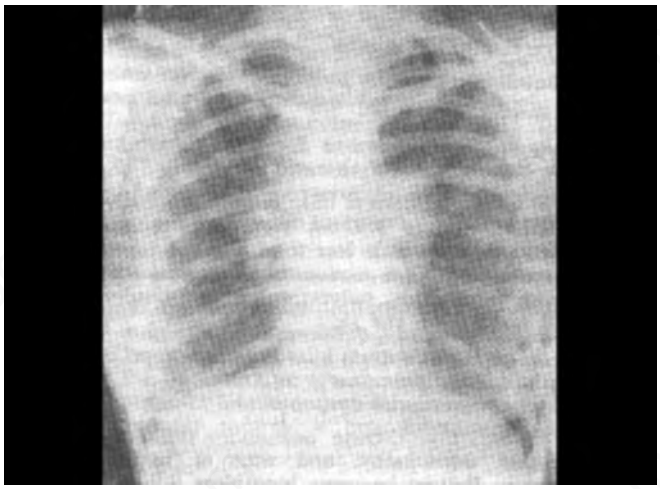


Fig. 24: HRCT chest axial view showing miliary tuberculosis

6. Catarrhal or influenzal – Repeated attacks of colds with run-down feeling, or failure to recover adequately from attack of influenza.
7. Haemoptysis – (a) May be due to pulmonary cavity. If a fairly large vessel is exposed within the cavity, small aneurysmal dilatations (Rasmussen's aneurysms) can result along the course of such a vessel, a rupture of which would cause a large haemoptysis. (b) From endobronchial tuberculous granuloma. (c) As a sequel of pulmonary. TB - (i) Persistence of open healed cavities in spite of therapy. (ii) Bronchiectasis of upper lobe. (iii) Secondary infection of a cavity (Aspergillus fumigatus). (iv) A broncholith (lymph node) extruded into a bronchus through blood vessels.
8. Non-resolving pneumonia.
9. Hoarseness of voice – due to laryngeal tuberculosis that occasionally complicates severe pulmonary infection.
10. Pleural – (a) Pleurisy dry or with effusion. (b) Spontaneous pneumothorax.
11. Traumatic – following injury to chest or "gassing".
12. Following certain diseases – such as measles, whooping cough, especially if complicated by bronchopneumonia.
13. Senile – Slow onset, symptoms of bronchitis or emphysema.
14. Asthmatic – Usually young patient starts getting attacks of so called "bronchial asthma" for the first time.
15. Amenorrhoea or oligomenorrhoea – may be the presenting symptom in young women.
16. Lymph node enlargement – including hilar, mediastinal and cervical groups or generalised with splenomegaly.
17. Initial presentation of AIDS in HIV-positive patients. (Most TB in such cases is reactivation of past infection).

SYMPTOMS AND SIGNS OF RESPIRATORY TUBERCULOSIS

See Table 39 for symptoms and signs.

Signs

- Localised wheeze
- Apical crackles
- Non-resolving pneumonia

Table 39: Symptoms and signs of respiratory tuberculosis
Symptoms
Asymptomatic
Cough
Expectoration (mucoid or purulent)
Haemoptysis
Fever and sweats
Malaise, fatigue
Chest wall pain
Dyspnoea due to extensive disease, pneumothorax or rapid development of pleural effusion.
Anorexia

Table 40: Complications
Pleural effusion
Empyema
Pneumothorax
Laryngitis
Enteritis as a result of swallowed sputum
Cor pulmonale from extensive disease and fibrosis
Adult respiratory distress syndrome
Mycetoma (*Aspergillus fumigatus*) in a healed open cavity

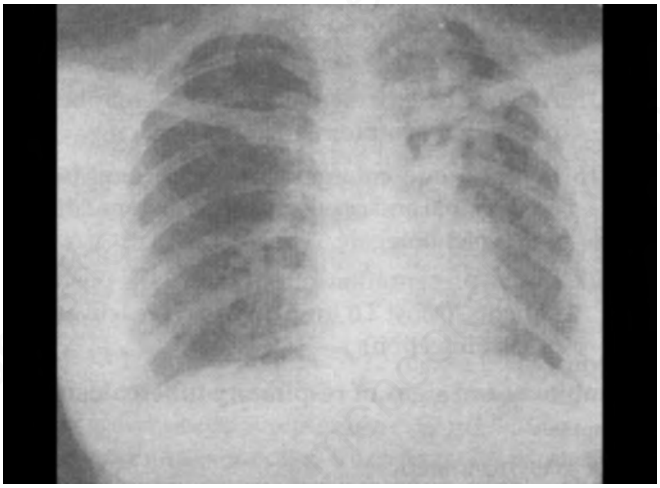


Fig. 25: Pulmonary tuberculosis – Lesion in left upper lobe with some shrinkage

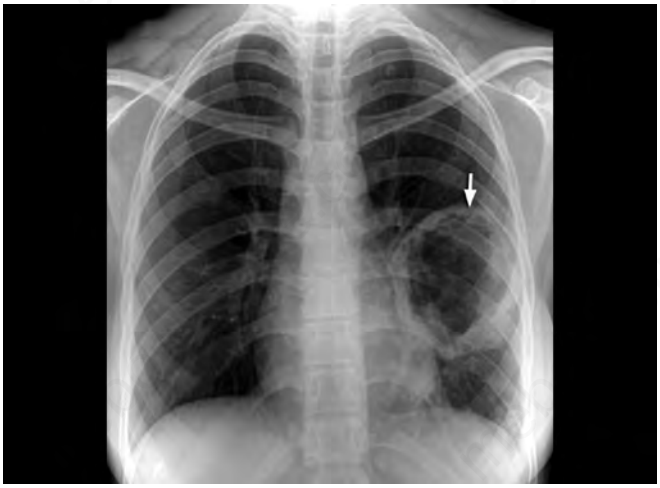


Fig. 26: X-ray chest showing a thick walled cavity

Complications

See Table 40 for complications.

Diagnosis

1. ***Isolation of mycobacterium*** – Repeated examination of sputum necessary. If sputum not available, laryngeal swabs, morning gastric lavage or specimens obtained by tracheobronchial suction are appropriate.
2. ***Chest radiograph*** – Common features:
   - Presence of opacities mainly in the upper zone, with a patchy or nodular appearance (Fig. 25).
   - Cavitation (Figs 26, 27 and 28).
   - Calcification
   - Dense nodular rounded or oval lesions (tuberculoma or bronchial cold abscess).
3. ***CT of the thorax*** – In miliary disease nodularity **(Figs 29 and 30)** may be better or sooner detected, and in TB with mediastinal lymphadenopathy.
4. ***Haematological*** – ESR usually increased. Haematological abnormalities in miliary disease.
5. ***Tuberculin testing – Mantoux test:***

Strength: 10 T.U. (0.1 mL) = 0.0002 mg of P.P.D. equivalent to 1:1000 dilution of old tuberculin

Reading taken: After 48 hours of intradermal injection See Table 41 for interpretation of Mantoux test.

6. ***Bronchoscopy*** – In patients with suspected TB but negative direct sputum specimens, fibreoptic bronchoscopic specimens for microscopy and culture (including transbronchial biopsy) may increase diagnostic yield.

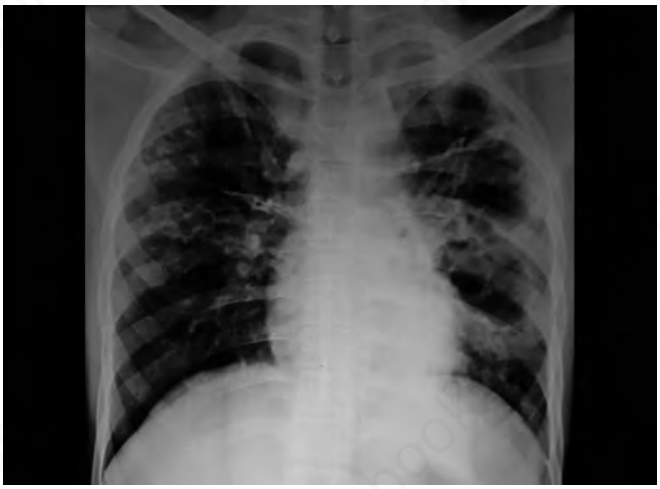


Fig. 27: X-ray chest showing a thick walled cavity

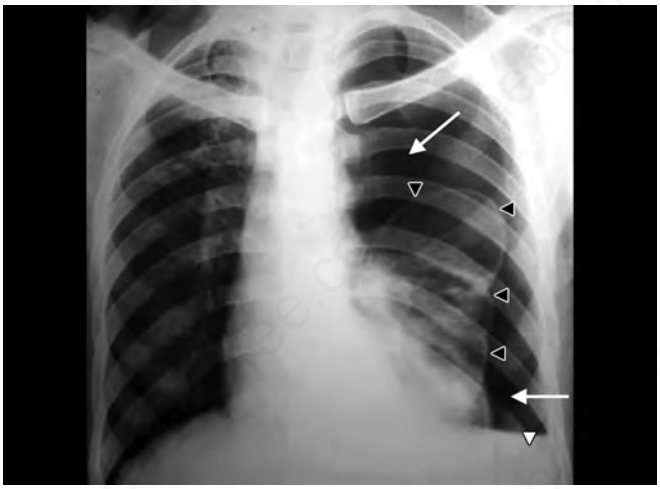


Fig. 28: X-ray chest showing hydropneumothorax (Arrow in the air, white arrowhead over fluid and black arrowhead showing collapsed lung)

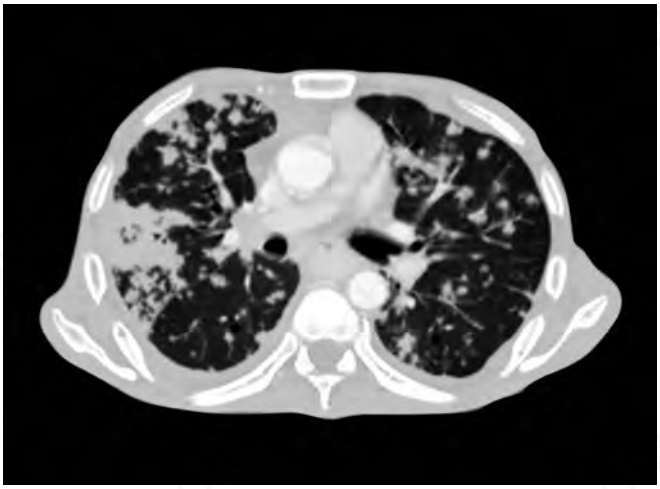


Fig. 29: Active pulm TB

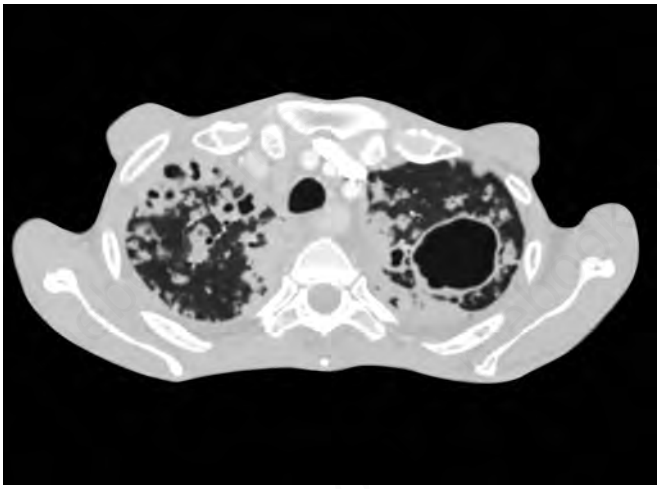


Fig. 30: Cavitating TB left apical

Table 41: Interpretation of Mantoux test

• Negative reaction	• Induration measuring <5 mm
• Doubtful reaction	• Induration measuring 6–9 mm
• Positive reaction	• Induration measuring >10 mm
• False-positive reaction	• Previous experience with atypical mycobacteria
• False-negative reaction	• Use of inactive PPD or improper deep injection into the skin, Viral infection
	• BCG vaccination, Miliary TB, Drugs
	• Steroids, Severe malnutrition, Neoplasms
	• Sarcoidosis, Immunosuppression.

7. ***Biopsy*** – Pleural biopsy is often helpful in diagnosis of pleural effusion.
8. ***Thoracotomy*** – TB is sometimes detected at thoracotomy for investigation of solid lesions.
9. ***Other diagnostic techniques*** – (a) *Serological* – Antigen detection by ELISA, competitive inhibition of the binding of monoclonal antibodies, immunoblotting techniques and agglutination-based tests. Antibodies have been detected in CSF, pleural fluid and bronchial washings. (b) *Polymerase chain reaction* (PCR) – For M.tuberculosis, the IS6110 DNA sequence is most commonly used. (c) *Restriction fragment link polymorphism* – variants of DNA restriction sites have been identified among

M. tuberculosis isolated by endonuclease restriction and electrophoresis.

Newer cultural techniques – BACTEC radiometric system. BACTE MGIT – Non radiometric system (mycobacteria growth indicator tube). It contains a special broth with florescence quenching-based oxygen sensor embedded at the bottom of the tube. When inoculated with MTB, consumption of dissolved O_2 produces fluorescence with UV light.

PCR – Can help to identify type of mycobacterium within 2 hours.

Interferon – Gamma (INF-γ) assays – (a) Quantiferon (b) T spot – TB test.

ELISA test for detection of anti-TB antibodies (TB IgM, TB IgA, TB IgG) sensitivity and specificity are not good.

NAAT (Nucleic acid amplification test) – Not only helps in diagnosis but also in detecting resistance by identifying specific genes.

Drug - resistant tuberculosis

DOTS: Emergence of MDR TB

The WHO TB control strategy, directly DOTS, consists of 5 components including administration of standardised short course chemotherapy regimens with first-line drugs under direct observation, at least in the intensive treatment phase, regardless of patient drug susceptibility pattern.

Treatment strategies for drug resistance TB (WHO)

Anti TB drugs are divided into first and second-line drugs. First-line therapy may not be sufficient in settings with a high degree of resistance to anti-TB drugs. In order to promote the programmatic treatment of MDR-TB in low income and middle-income countries that have adopted the DOTS strategy, the WHO have been evolving the DOTS-Plus for MDR-TB programmes.

See Table 42 for the comparison of DOTS and DOTS-Plus strategies.

Table 42: Comparison of DOTS and DOTS-Plus strategies

DOTS	*DOTS-Plus*
• Political and administrative commitment • Good-quality diagnosis by sputum microscopy • Uninterrupted supply of first-line drugs for standardized treatment through outpatient therapy • Directly observed treatment • Systematic monitoring and accountability	• Sustained political and administrative commitment • Accurate, timely diagnosis through quality-assured culture and drug susceptibility testing • Uninterrupted supply of first and second-line drugs, utilizing the latter under strict supervision • Directly observed treatment • Standardized recording and reporting system that enable performance monitoring and evaluation of treatment outcome

DIAGNOSIS

1. *Clinical:* (a) No visible clinical improvement in spite of regular and adequate chemotherapy for 3 months. (b) Presence of multiple or giant cavities. (c) Serial X-rays showing deterioration or no improvement after 3 months of therapy. (d) 'Fall and rise' phenomenon in which direct sputum smear examination initially shows a fall in number of bacteria followed by a gradual rise in count due to rise of resistant organisms.
2. *Laboratory:*(a) Sputum is positive by direct smear even after 5 months of adequate therapy. (b) Culture and sensitivity test of the bacilli by slide culture, use of egg enriched sheep blood media (FESBM), Bactec system of radiometric detection of mycobacterial growth, Luciferase Reporter Mycobacteriophase test (LRM test). (c) Gen box detects MR TB in 2 hours.

MANAGEMENT

Drugs used in primary chemotherapy are listed in Table 43 and regimes under DOTS in Table 44.

Prolongation of continuation phase

For 12 months for:

- CNS and TB meningitis
- Localized disease in intractable drug-resistant infection

Second-line antitubercular drugs

These are listed in Table 45.

Multidrug-resistant-TB management:

See Table 46 for the fundamental aspects of MDR-TB.

MDR-TB is defined as tuberculosis disease where bacilli are resistant to Isoniazid and Rifampicin, with or without resistant to other organism.

XDR-TB (Extensively drug resistant TB) is a subset of MDR-TB where bacilli, in addition to being resistant to Rifampicin and Isoniazid, are also resistant to fluoroquinolones and any one of the second line injectable drugs (Kanamycin, Capreomycin and Amikacin).

DST: Drug-sensitivity test : E: Ethambutol; FLd : First-line drug; FQ: Fluoroquinolone; H: Isoniazid; Km: Kanamycin; MDR: Multidrug-resistant; R: Rifampicin; SLD: Second-line drug, Z: Pyrazinamide

Table 43: Drugs for primary chemotherapy (First-line drugs)

Drug	*Daily Dose (Adult)*	*Thrice Weekly Dose*	*Toxicity/Precautions*
Rifampicin	>50 kg 600 mg <50 kg 450 mg.	(10 mg/kg) (10 mg/kg)	Urine coloured pinkish-orange. Hepatitis, rash.
Isoniazid	200–300 mg (In miliary TB 10 mg/kg)	(5 mg/kg) (10 mg/kg)	Fever and rash. Peripheral neuropathy, hepatitis. Pyridoxine 10 mg advised for patients at risk of peripheral neuropathy (diabetes, chronic renal failure, malnutrition).
Pyrazinamide	>50 kg 2 gm. (25 mg/kg max 2 gm) <50 kg 1.5 gm	(35 mg/kg, max 3 gm)	Arthralgia, hyperuricemia, photosensitivity. Biochemical evidence of hepatitis
Ethambutol	25 mg/kg in initial phase,	(30 mg/kg) 15 mg/kg in continuation phase	Optic neuritis. (Not to be given to young children, elderly and in renal failure).

Table 44: Under DOTs following treatment regimen are used

	Indication	*Intensive Phase*		*Continuation phase*	
		Drugs	*Duration*	*Drugs*	*Duration*
Category I	New sputum smear-positive New sputum smear-negative New extra-pulmonary tuberculosis	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	Thrice weekly for 2 months	Isoniazid and Rifampicin	Thrice weekly for 4 months
Category II	Sputum smear-positive relapse Sputum smear-positive failure Sputum smear-positive treatment after default	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin	Thrice weekly for 2 months followed by		
		Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	For 1 month	Isoniazid, Rifampicin and Pyrazinamide	5 months

Table 45: Second-line antituberculous drugs.

Drug	*Dose*
Streptomycin	20-40 mg/kg/day od im
Kanamycin	15-30 mg/kg/day od im
Amikacin	15-22.5 mg/kg/day od im
Capreomycin	15-30 mg/kg/day od im
Ofloxacin	15-20 mg/kg/day bd orally
Levofloxacin	7.5-10 mg/kg/day od orally
Moxifloxacin	7.5-10 mg/kg/day orally
Ethionamide	15-20 mg/kg/day bd orally
Prothionamide	15-20 mg/kg/day bd orally
Cycloserine*	10-20 mg/kg/day od or bd orally
PAS*	150 mg/kg/day bd or tds orally

*Cycloserine and PAS are bacteriostatic others are bactericidal.

Table 46: Fundamental aspects of MDR-TB

Step	*Considerations*
1. Diagnose	Compile and compare information History of drugs: 1 month intake of a failed drug regimen could be a strong predictor of resistance DST: most reliable for R and H; also reliable for Km and FQ; less reliable for E and Z; very low reliability for group 4 drugs
2. Number of drugs	At least four effective drugs
3. Drugs selection	Use FLDs if they are still effective One injectable Use group 5 drugs until complete for effective drugs If necessary, use group 5 drugs to strengthen the regimen, or when no four effective drugs are reached with the previous groups
4. Length of the injectable	At least 4 months after smear or culture conversion; longer if there are no three effective drugs during continuation phase or are from group 5
5. Surgery	Consider only if: • Few effective drugs are available • Localized lesions • Sufficient respiratory reserve
6. Ideal regimen	Standardized: if there is no use of SLDs in the past Individualized: use of SLDs the past or contact of a MDR-TB patient who had use of them (treat with the effective regimen of the index case)

Treatment Regimen under RNTCP for MDR-TB and XDR-TB

For MDR-TB

Six drugs in intensive phase for 6–9 months: Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide and Ethambutol.

Four drugs in continuation phase for 18 months: Levofloxacin, Ethionamide, Cycloserine and Ethambutol

Reserve drug p-aminosalicylic acid.

For XDR-TB

Seven drugs in intensive phase for 6–12 months: Capreomycin, p-aminosalicylic acid, Moxifloxacin, high dose Isoniazid, Clofazimine, Linezolid, Amoxicillin and clavulinic acid.

Six drugs in continuation phase for 18 months: p-aminosalicylic acid, Moxifloxacin, high dose Isoniazid, Clofazimine, Linezolid, Amoxicillin and clavulinic acid.

Reserve drugs: Clarithromycin, Thiacetazone

1. **Corticosteroids**–

   Indications for corticosteroids in tuberculosis are listed in Table 47.

2. **Consider only if**
   - Few effective drugs are available
   - Localized lesions
   - Sufficient respiratory reserve

3. **Surgery** - Surgical resection of infected lobe if feasible.

4. **Symptomatic treatment**
   a. Cough – If irritative, linctus codeine. No smoking if associated catarrh or laryngitis.
   b. Haemoptysis (Refer).
   c. Laryngitis – Rest to the voice. If pain, anaesthetic powders, sprays or lozenges. Injection of alcohol into superior laryngeal nerve will give temporary relief.

Treatment in HIV-infected patients – HAART can be delayed if CD4 counts > 200 µL until antituberculous therapy is completed. In those with CD4 count < 200 µL, HAART should be started within 2 months of starting antituberculous therapy, to prevent a further AIDS-defining event.

Table 47: Indications for corticosteroids in tuberculosis

Tuberculous pneumonia
Miliary tuberculosis
Widespread infiltration
Pleural, pericardial or peritoneal effusion
Acutely ill patients
Segmental opacities in primary pulmonary tuberculosis of less than 3 months duration thereby significantly lowering incidence of bronchiectasis
Suppression of hypersensitivity reaction to anti-tuberculous drugs
Tuberculous meningitis
Large lymph nodes involving or compressing trachea or bronchi

TB immune reconstitution inflammatory syndrome (IRIS) is a relatively frequent complication in HIV-TB-coinfected patients after they start highly active antiretroviral therapy (HAART). There are two forms of TB IRIS: The 'paradoxical' type (clinical worsening of a patient on TB treatment) and the 'unmasking' type (undiagnosed TB becoming apparent after starting HAART). The pathogenesis appears to be IRIS following initiation of HAART is accompanied by an increase in immune responses to *Mycobacterium tuberculosis*. Diagnosis of IRIS include a low CD4 lymphocytic count, disseminated and a short interval between TB treatment and HAART initiation.

Drug resistance. Primary and acquired drug resistance is an increasing problem. A positive culture is the only means of determining drug susceptibilities. A history of prior treatment increases likelihood of drug resistance tenfold. Multi-drug resistant TB (MDR-TB) is defined as high resistance to rifampicin and isoniazid ± other drugs (> 5%). Molecular probes for rifampicin resistance should be undertaken in patients in whom treatment has failed or who have been treated previously. Management of MDR-TB requires reserve drugs, and may last for up to 2 years. Non-MDR-TB resistant cases should be followed-up for one year after cessation of treatment, and MDR-TB indefinitely.

Chemoprophylaxis – Drug treatment is given to destroy or diminish bacterial populations and thus prevent clinical disease.

Primary chemoprophylaxis – (before evidence of infection) is required in children under age of 2 years who are close contacts of sputum smear-positive individuals. Isoniazid 5 mg/kg is given immediately and continued until serial tuberculin testing at a 6–8 week interval. If the initial or repeat test is positive, isoniazid for 6 months, or isoniazid 5 mg/kg and rifampicin 10 mg/kg for 3 months. If serial tuberculin tests are negative, isoniazid can be stopped and BCG vaccination performed, if not already given.

Secondary chemoprophylaxis – is to prevent progression to clinical disease in infected (tuberculin positive, but not following BCG), e.g. (a) Children under 5 years of age because of risk of miliary disease and meningitis. (b) Tuberculin-positive children and adults upto 35 years of age (who have not had BCG) in close contact with respiratory cases. (c) Recent tuberculin convertors. (d) Patients on long-term corticosteroid or immunosuppressive drug therapy. Either Isoniazid 5–10 mg/kg (maximum 300 mg.) for 6 months, or Rifampicin 10 mg/kg and Isoniazid 5–10 mg/kg for 3 months is advised. In HIV-positive patients with positive tuberculin test (who have not had BCG in the past), Isoniazid 5 mg/kg (upto 300 mg), should be continued indefinitely.

OPPORTUNISTIC MYCOBACTERIAL INFECTIONS

Common species: M. kansasii, M. avium intracellular, M. malmoense and M. xenopi.

Clinical features: More than 50% have pre-existing pulmonary disease, usually COPD and/or old pulmonary T.B. M. kansasii, is associated with occupational dust exposure and MAC with HIV/AIDS. Onset of symptoms is gradual with cough, sputum, haemoptysis, malaise, breathlessness, wt. loss. Radiological appearances are similar to those of the infiltrates and cavities of M. tuberculosis infection. Cavitation is seen in 60–80% of patients.

Diagnosis depends on culture and special means of identification (e.g. temperature range, oxygen preference, pigment production, hydrolysis of Tween 80, chromatography). DNA probes are available for MAC, M. kansasii and M. gordonae. Disease is diagnosed when cultures from two or more specimens taken more than 7 days apart are positive in a patient in whom chest radiography suggests mycobacterial infection.

Management – Rifampicin and ethambutol is the combination irrespective of results of *in vitro* sensitivity tests. There is synergism between these drugs and also between these drugs and streptomycin. In HIV/AIDS patients prophylactic clarithromycin protects against MAC, but such monotherapy risks development of resistance.

11. PULMONARY EOSINOPHILIA

A group of diseases in which the pulmonary pathology (commonly eosinophilic consolidation) manifests as fleeting shadowing on chest radiograph, is associated with raised blood eosinophil count in which more than 6% of the leucocytes are eosinophils (>0.4×10^9/litre) (Table 48). Lung infiltration with eosinophils, shown on lung biopsy or BAL, may occur with a normal eosinophil count. Conversely, a moderately raised eosinophil count may be a feature of several lung diseases with a non-eosinophilic pathology.

Table 48: Causes of eosinophilic lung diseases
Atopic allergy
• Asthma
• Allergic bronchopulmonary aspergillosis
Pulmonary diseases with likely blood eosinophilia
• Sarcoidosis
• Tuberculosis
• Lung cancer
• Lymphoma, leukaemia
• Fibrosing alveolitis
Helminth infections
• Microfilaria
• Schistosoma spp.
• Ascaris lumbricoides
• Toxocara canis
Drugs
• Nitrofurantoin
• Tetracycline
• Sulphonamides
• Chlorpropamide
• Sodium aminosalicylate
• Imipramine
• Penicillins
Other ingestants
• Toxic oil syndrome
• (Distilled aniline, denatured rape-seed oil)
• Eosinophilic myalgia syndrome
• (Bacterial contaminant in L-tryptophan preparations)
Idiopathic
• Simple pulmonary eosinophilia (Loeffler's syndrome)
• Chronic eosinophilic pneumonia
• Acute eosinophilic pneumonia
• Allergic granulomatosis (Churg-Strauss syndrome).
• Idiopathic hypereosinophilic syndrome

TROPICAL PULMONARY EOSINOPHILIA (TPE)

A syndrome characterised chiefly by cough, paroxysms of dyspnoea, a raised white cell count with persistent and absolute eosinophilia, and often systemic manifestations such as fever, loss of weight and lassitude.

Causation

TPE has been considered to be hypersensitive reaction to filarial antigen because – (a) Microfilaria have been demonstrated in lung, liver and lymphnodes. (b) High filarial antibody titres are found in patients and the titre decreases after cure. (c) Responds to antifilarial therapy.

Symptoms

ONSET– Slow and insidious with symptoms of asthmatic bronchitis. Rarely sudden onset with fever, headache and bodyache.

1. *Cough* – Most prominent symptom. In early stages dry, hacking. Later on paroxysmal and worse at night, especially early hours of morning. Sometimes no cough during day. Blood streaking of sputum not uncommon after paroxysm of cough. Rarely haemoptysis.
2. *Expiratory dyspnoea* – As paroxysms of cough become more frequent they are followed by wheezing and expiratory dyspnoea. Attacks simulating bronchial asthma may occur.
3. *Fever* – Common, 99 to 101°F. Usually continuous. Occasionally relapsing or intermittent. May rise to 104°F initially following treatment.
4. *Loss of weight* – Usually with onset of disease. Poor appetite and disinclination for evening meal in order to check cough at night.
5. *General weakness and exhaustion.*
6. *Pain in chest* – Common symptom in adults, usually substernal and dull aching.
7. *GI symptoms* – Attack of vomiting following paroxysm of cough common in children. Sometimes diarrhoea.
8. *Haemoptysis* – may occur in thehyperacute form of the disease.

Signs

1. *Of asthmatic bronchitis* – With hyperresonance of chest, prolonged expiration and wheeze and crackles at bases.
2. *Sputum* – Scanty and viscid. Clumps of eosinophils.
3. *Spleen* – may be enlarged.
4. *Lymphadenopathy* – Often generalized.

Diagnosis

1. *White cell count* – 20,000–50,000/c.mm, eosinophils 20–90%. Absolute eosinophil count more than 2,500 per c.mm. Eosinophilic count is disproportionately elevated in chronic eosinophilic pneumonia.
2. *Filarial complement fixation test* – positive.
3. *Chest radiograph* – (a) Diffuse mottling of the lungs usually bilateral and symmetrical, coarser than miliary tuberculosis, or (b) prominent linear striations radiating from hilum, or (c) diffuse fan-shaped streakings, or (d) ground glass appearance or cotton wool appearance Figure 31.

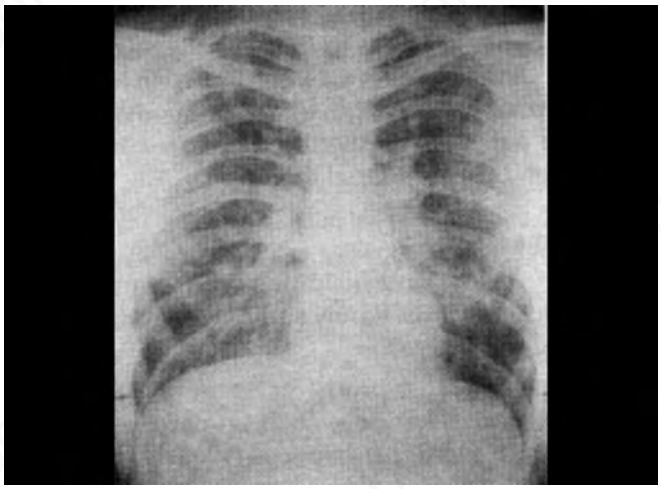


Fig. 31: Diffusely distributed patches of density in pulmonary eosinophilia

Table 49: Criteria for diagnosis of ABPA

A. Main diagnostic criteria
• Asthma
• Chest radiograph change (infiltrates, segmental lobar collapse)
• Positive skin test/radioallergosorbent test for A. fumigatus
• IgG precipitating antibody to A. fumigatus
• Raised serum IgE (often >2000 IU/mL)
• Blood eosinophilia
• Proximal bronchiectasis
B. Other diagnostic features
• History of brownish plug in sputum
• Culture of A. fumigatus from sputum
• Elevated IgE (and IgG) class antibodies specific for A. fumigatus

4. *IgE* – (a) Total IgE and blood eosinophilic count are elevated proportionately in helminth infections. (b) Total IgE is disproportionately elevated in allergic bronchopulmonary mycoses.

Treatment: Diethylcarbamazine 50 mg qds. for one month. Three such courses can be repeated at monthly intervals to prevent relapse.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

APBA is the most common eosinophilic lung disease in temperate climates. Inhalation of spores of the microscopic fungus *Aspergillus fumigatus* by an allergic individual causes bronchial, peribronchial and/or alveolar eosinophilic pulmonary infiltrates. Fungal hyphae develop within the bronchial lumen mucus, leading to mucus plugging, bronchial wall thickening, fibrosis and bronchiectasis.

Eosinophilic pneumonia may cause infiltrates seen on chest radiography, and organizing exudate may cause bronchial obstruction and segmental/lobar collapse. Acute ABPA is clinically silent or causes fever, malaise, worsening asthma and plug expectoration. Criteria for diagnosis of ABPA is given in Table 49.

MANAGEMENT – *For acute ABPA:* Prednisolone 30 mg/day, until infiltrates have gone, dose tapered to zero over few weeks.

Recurrent disease: Persistent episodes may lead to – (a) Proximal bronchiectasis of saccular type. (B) Upper lobe fibrosis. Cavitation and mycetoma occur late. (c) Chronic fixed airway obstruction may occur as a consequence of lung fibrosis. Treatment – Intermittent corticosteroids. Systemic antifungal drugs (e.g. itraconazole 220 mg or ketoconazole 200 mg daily) for 2 weeks may reduce requirement of a long-term corticosteroids.

Simple pulmonary eosinophilia (Loeffler's syndrome) comprises transient, bilateral, eosinophilic peripheral lung infiltrates, modest blood eosinophilia (<1500/μL) and few or no symptoms. In about 1/3 of patients there is no recognizable cause; infiltrates subside spontaneously in 2–4 weeks and do not require treatment.

Chronic eosinophilic pneumonia has an insidious onset with cough, fever, breathlessness and wt. loss. It is more common in women. One half of patients have asthma, and more than 80% peripheral eosinophilia (mean eosinophilic count 30% of total WBC count). Biopsy shows eosinophilic infiltration of the interstitium and alveoli with fibrosis. BAL shows gross eosinophilia (>60%), highly suggestive of the diagnosis. Two thirds of patients have high total serum IgE.

Chest radiograph (Fig. 32) – Peripheral patchy consolidation most common in upper and mid zone ('negative image of pulmonary oedema'). Cavitation and pleural effusion may occur and CT may show mediastinal lymphadenopathy. Lung function tests show restrictive disease. Respiratory failure may occur in severe cases.

Management – Prednisolone 30–40 mg/day produces immediate improvement, to be continued for at least 12 months.

Acute eosinophilic pneumonia is rare. It is an acute version of chronic eosinophilic pneumonia, comprising

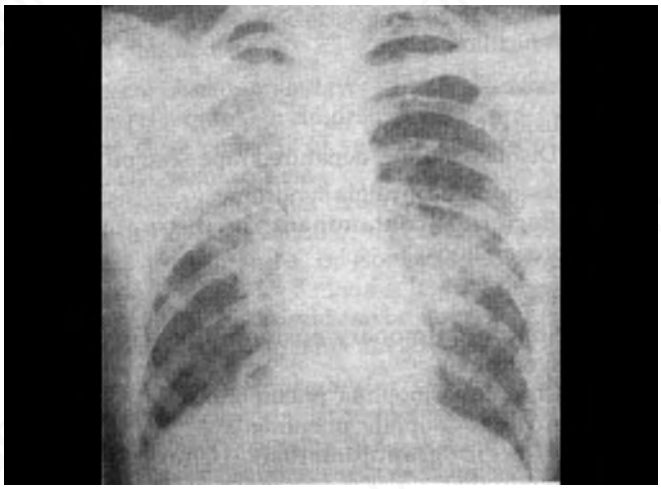


Fig. 32: Eosinophilic pneumonia

a febrile illness of less than 5 days duration, hypoxemic respiratory failure, eosinophils on BAL. Chest radiograph does not show peripherally based infiltrates. Peripheral blood eosinophilic count is usually normal. No infectious agent has been shown to cause the disease.

Chronic eosinophilic pneumonia (Carrington's disease). CEP is a disease of unknown aetiology with accumulation of eosinophils in the lungs.

Cl Fs. - Gradual onset with cough, dyspnoea and wt. loss, X-ray chest – Bilateral peripheral shadows at times migratory. Eosinophils > 1000 mm^3. BAL Eosinophils > 40% of other fluid cells. Treatment long-term steroids.

Eosinophilic granulomatosis with polyangiitis (EGPA) (earlier called Churg-Strauss syndrome) is a rare disease seen in patients with asthma. It comprises multiorgan, necrotizing small or medium vessel arteritis (Table 50).

Treatment – Corticosteroid with or without cyclophosphamide for at least one year.

Idiopathic hypereosinophilic syndrome is rare, and appears to be caused by fusion protein which produces persistently active tyrosine kinase. Eosinophil count is raised to more than 1500/mL for more than 6 months and eosinophils often constitute more than 30–70% of the total WBC count. The marrow exhibits eosinophilic infiltration. Pulmonary manifestations are cough, malaise, infiltrates and effusions. The heart and major arteries are affected, causing CHF, dysrhythmias, endomyocardial fibrosis and arterial thrombosis.

Treatment – Corticosteroids, cytotoxic drugs and interferon-α. Some patients may respond to imatinib mesylate (a tyrosine kinase inhibitor).

Table 50: Features of eosinophilic granulomatosis with polyangiitis

• Several years' asthma ± other atopic disease
• Peripheral blood eosinophilia (usually >1.5x109/L)
• Pulmonary infiltrates usual
• High IgE
• High eosinophil levels on BAL
• Antineutrophil cytoplasm antibody positive in 50%
• Multisystem involvement due to vasculitis
• Upper respiratory tract (sinusitis, polyps)
• Skin (nodules, purpura) – 70%
• CNS (mononeuritis multiplex) – 65%
• GI tract (pain, bleeding, diarrhoea) – 60%
• CVS (pericarditis – 30%, CHF – 50%)
• Kidney impairment – 50%

HELMINTHIC PE

Ascaris lumbricoides. Simple pulmonary eosinophilia caused by an allergic reaction in the lung to the migrating larvae of A. lumbricoides. Migration occurs 10–16 days after egg ingestion, and the larvae lodge in pulmonary capillaries, a T cell-dependent eosinophilic reaction ensues. Cough and malaise may occur, but illness settles spontaneously over a few days or weeks.

Other parasites, notably Wuchereria bancrofti, Brugia malayi and other parasites (e.g. A. duodenale, Strongyloides, Toxocara canis) can cause a more severe illness sometimes termed 'tropical pulmonary eosinophilia'.

Drugs and toxins. Several drugs can cause pulmonary eosinophilia with or without cough and breathlessness. Most common are nitrofurantoin, sulphasalazine, NSAIDs, antibiotics (e.g. ampicillin, oxytetracycline) and antineoplastic drugs (e.g. bleomycin, methotrexate). Toxins have included contaminated L-tryptophan and rape seed oil contaminated with oleoalanide (marketed as olive oil).

12. LUNG CANCER

AETIOLOGY

Age – chiefly 40 to 55. *Sex* – More common in males.

Predisposing Factors

- Cigarette smoking – Risk of bronchogenic carcinoma varies directly with the number of cigarettes smoked. After stopping smoking, the risk declines rapidly and after 10 years approaches that of non-smokers.

Passive smokers (e.g. non-smokers living with a smoker) appear to have double the risk of developing lung cancer.

- Occupational exposure – to radioactive gases, asbestos, arsenic, nickel, chromates, metallic iron and iron oxides, coal gas manufacture.
- Atmospheric pollution – Urban malignancy twice that of rural areas.
- Lung disease – Risk of lung cancer is greatly increased in patients with cryptogenic fibrosing alveolitis. Also in alveolitis of systemic sclerosis and other types of active alveolitis.

CELL TYPES

Squamous cell carcinoma arises in large airways, grows relatively slowly, metastasizes less.

Adenocarcinoma is more commonly peripheral and is found more often in non-smokers. Bronchoalveolar cell carcinoma grows diffusely within a lobe using the alveolar walls like a trellis. This becomes coated with malignant cells, and it may mimic slowly progressive or non-resolving pneumonia.

Large cell and anaplastic carcinoma. Its behaviour is intermediate between squamous and small cell carcinoma.

Small cell carcinoma is highly malignant and rapidly growing. It typically arises as a relatively small central airway tumour that metastasizes early to thoracic nodes. Almost all patients have metastases at time of presentation.

SYMPTOMS

I. Non-specific– Weakness, loss of weight, tiredness, anorexia and fever.

II. Respiratory (local or primary) symptoms:

1. *Cough* – Affects majority of patients and is often associated with influenza-like illness or pneumonia distal to the obstruction caused by a tumour. Increasing persistence of cough is the most common symptom.
2. *Haemoptysis*– is usually mild and may be only occasional.
3. *Dyspnoea* – is usually associated with increased cough and sputum.
4. *Chest pain* – may be: (a) intermittent discomfort or pain on same side as lesion, usually worse at night, (b) pleural pain from local pneumonia or carcinomatous involvement of pleura, or (c) persistent, severe localized pain with radiation along distribution of intercostal nerve.
5. *Wheeze* – Some patients may notice a localized unilateral wheezing due to the tumour narrowing a main airway.

III. *Metastatic symptoms:*

A. INTRATHORACIC:

1. *Nerves* – (a) Phrenic nerve – iiccough, paresis of diaphragm. (b) Recurrent laryngeal nerve – Hoarseness or aphonia, bovine cough. (c) Cervical sympathetic – Horner's syndrome. (d) Vagus – Gastric symptoms. (e) Brachial plexus – Lower part involvement with pain around shoulder joint and in arm with sensory impairment along ulnar border of forearm and hand and development of muscular weakness and wasting. (f) Intercostal nerve – Severe pain along distribution of the nerve.
2. *Oesophagus* – Dysphagia.
3. *Vessels* – (a) Superior vena cava – Venous engorgement of head and neck. (b) Azygos vein – Dilatation of superficial veins on thorax. (c) Thoracic duct – Chylous effusion. (d) Axillary vessels – Loss of peripheral pulses and oedema of arm.
4. *Erosion of rib* – Local pain and bony tenderness.
5. *Invasion of heart and pericardium* – resulting in arrhythmias, or signs of pericardial effusion and CHF.

B. EXTRATHORACIC METASTASES:

1. Intracranial.
2. Bony metastasis predominantly in ribs, vertebrae, humeri and femora with pain as the presenting symptom.
3. Hepatic metastasis often silent.
4. Suprarenal metastasis seldom result in clinical Addison's disease.

IV. *Symptoms due to non-metastatic extrapulmonary manifestations:*

- *Endocrine and metabolic* – (a) Cushing's syndrome (ACTH) commonest, (b) Dilutional hyponatremia (SIADH), (c) Hypercalcemia (Osteolytic secondary to PTH), (d) Hypoglycemia (insulin), (e) Hyperthyroidism (TSH), (f) Gynaecomastia.
- *Skeletal* – Clubbing, hypertrophic pulmonary osteoarthropathy in which finger clubbing occurs with painful swelling of the wrists and often the ankles and periosteal new bone formation occurs on the tibia, fibula, radius and ulna.

Table 51: Differential diagnosis of lung Ca on radiography
Slowly resolving bacterial pneumonia
Lobar collapse from mucus impaction
Bronchial symptoms caused by a benign tumour
Peripheral mass or masses caused by metastasis from an abdominal primary (e.g. kidney carcinoma)
Pulmonary embolism
Endobronchial tuberculosis
Lymphoma
Pleural effusion from other malignancies (e.g. breast and ovary)
Lung abscess (cavitating tumour with necrosis can mimic lung abscess)
Diaphragmatic paralysis caused by phrenic nerve damage (e.g. thoracic trauma, neuralgic amyotrophy)

- *Skin* – Acanthosis nigricans, pruritus, eczematoid and bullous rashes.
- *Neurological* – (a) Encephalopathy with dementia, cerebellar damage or leucodystrophy. (b) Cerebellar degeneration syndrome. (c) Extra-pyramidal syndrome. (d) Myelopathy. (e) Neuropathy. (f) Myasthenic (Eaton-Lambert) syndrome is exclusive to small cell tumours and may precede detection of the tumour by between 6–12 months. (g) Motor neuron disease.
- *Renal* – Nephrotic syndrome.
- *Muscular* – Polymyositis, dermatomyositis.
- *Vascular* – Thrombophlebitis migrans, non-bacterial endocarditis.
- *Haematological* – Haemolytic anaemia, thrombocytopenia, red cell aplasia, eosinophilia.

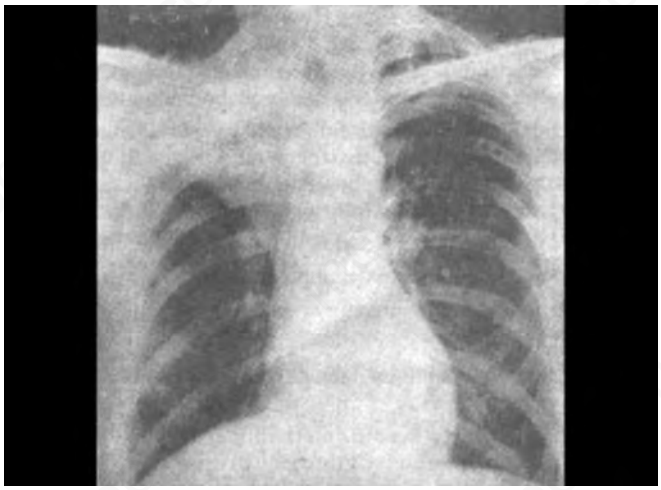


Fig. 33: Collapse and consolidation of right upper lobe with some central transradiancy in area of necrosis

SIGNS

- Finger clubbing (80% of cases)
- Palpable supraclavicular nodes
- Mid-inspiratory crackles over a lobe, reduction in breath sounds over a lobe and signs of lobar collapse, which results from bronchial obstruction.
- Wheeze: Near-obstruction of a lobar or segmental airway may cause fixed, monophonic wheeze, near-obstruction of a main bronchus or trachea causes stridor.
- Pleural effusion, rib or back tenderness and SVC obstruction.

Pancoast tumour– A tumour at the apex of the lung may invade locally and produce Pancoast syndrome:

- Pain in the shoulder or upper anterior chest or between the scapulae, spreading to the arms once brachial plexus gets involved.
- Weakness and atrophy of muscles of hand
- Horner's syndrome
- Hoarseness

DIAGNOSIS

1. ***Chest radiography***– Types of lesions (Table 51 for differential diagnosis):

- Peripheral single mass. May be fairly well defined or more often irregular with 'pseudopodia' or 'sun ray' projections radiating from its surface (Fig. 33) or diffuse multinodular lesion or infiltrate (Fig. 34).
- Collapse and/or consolidation of a lobe or segment with or without a hilar mass indistinguishable from simple pneumonia.

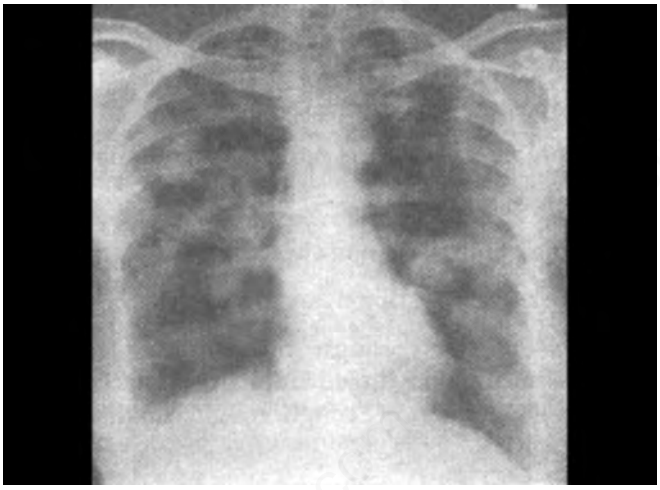


Fig. 34: Multiple pulmonary cannon ball metastases. A case of hepatocellular carcinoma. Other sources of such metastases may be malignant renal and adrenal tumours, malignant testicular tumours, or prostatic carcinoma

- Pleural effusion – because of direct pleural invasion by tumour or increase in lymphatic pressure by compression of draining lymphatics at the hilum.
- Hilar and/or mediastinal enlargement – due to lymph node spread from primary site.
- Elevation of hemidiaphragm
- Rib destruction due to direct invasion of chest wall or osteolytic lesions of the ribs from metastatic spread.
- Lung abscess – due to breakdown of tumour or infection of the lung beyond the malignant obstruction.

(For causes of multiple pulmonary nodules see Chapter 16).

2. ***CT*** – Thoracic CT including the upper abdomen is an essential investigation in all cases.

When possible CT should be undertaken before bronchoscopy because this is guided by the results. CT scan. Useful (i) for tumoursize, (ii) for CT guided biopsy of suspected lesion. For nodules between 8 and 10mm, a biopsy may be attempted if the nodule is accessible. Use of CT fluoroscopy makes it easier to track the course of the biopsy cannula and needle, (iii) to assess response to treatment.

3. ***Bronchoscopy*** – Fibre-optic bronchoscopy has replaced sputum cytology as the usual method of cytological/histological support for the diagnosis.
4. ***Sputum cytology*** – Studies of sputum and bronchial washing for cancer cells.
5. ***Needle* biopsy** – Peripheral lung tumors are not visible at bronchoscopy and percutaneous fine needle biopsy is required for its diagnosis. Fine needle biopsy is also helpful for sampling supraclavicular or other nodes, skin deposits and possible liver or adrenal metastasis, and pleural biopsies in case of pleural effusion.
6. ***CT Scan positron imaging tomography*** – PET is more sensitive and more specific than CT for detection of metastases in intrathoracic lymphnodes and distant organs. It is particularly useful for examining enlarged mediastinal nodes. PET in combination with CT (CT-PET) is a definitive staging technique.
7. ***Endoscopic oesophageal ultrasonography*** – with needle aspiration is a non-invasive procedure for exploring especially the left side of the mediastinum.

MANAGEMENT

The most important factors which influence the choice of therapy are the histological cell type and the stage of the disease. Squamous cell carcinomas are relatively slow growing, tend to remain more localized and carry the best prognosis. On the other hand, small cell tumours disseminate early and widely and should be considered for multiple drug chemotherapy, with or without radiotherapy. Prognosis for adenocarcinomas and large cell carcinomas lies in between these two cell types (Figs 35 and 36).

1. ***Surgery*** – *Indications* – Factors in assessing suitability for surgery include – age of the patient, lung function, hilar and mediastinal node involvement, absence of extrathoracic disease and histological cell type. Surgery is most likely to be curative for non-small cell lung cancer. *Contraindications* – (a) Distant metastasis. (b) Mediastinal involvement – Vocal cord paralysis, vena cava obstruction, oesophageal involvement, positive scalene node biopsy, involvement of carina or trachea, blood stained pleural effusion. (c) Poor respiratory function. (d) Advanced age. (e) Most small cell carcinomas. (f) Extension to chest wall.

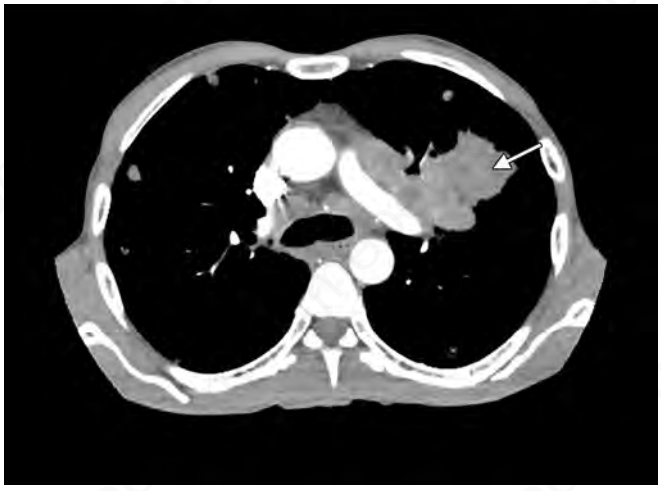


Fig. 35: Carcinoma of bronchus mediastinal window CT chest axial view

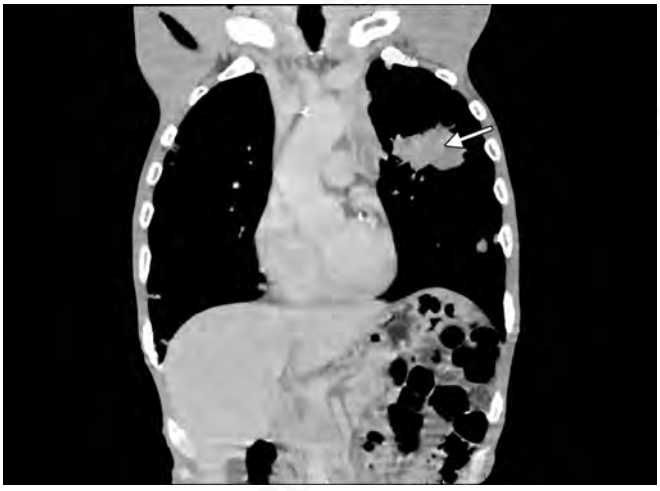


Fig. 36: Carcinoma of bronchus mediastinal window CT chest coronal view

2. ***Radiotherapy*** – Best indication is inoperability or operable tumour where resection is not carried out for other reasons (e.g. COPD, heart disease). Helpful palliative for distressing symptoms such as haemoptysis, cough and chest pain. Can temporarily relieve superior vena cava obstruction, or compression of oesophagus or major bronchus. Continuous hyperfractional accelerated radiotherapy (CHART) three times daily over 2 weeks improves chances of survival.
3. ***Chemotherapy*** – Is particularly useful for patients with wide-spread disease and no local symptoms (e.g. haemoptysis) requiring urgent palliative radiotherapy. Commonly used combinations include mitomycin-ifosfamide-cisplatin, mitomycin-vincristine-cisplatin, cisplatin-gemcitabine and cisplatin-vinorelbine. Three cycles are given.

PARANEOPLASTIC SYNDROME

(Notably Eaton-Lambert syndrome and pulmonary osteoarthropathy) improve when the primary tumour is removed. More commonly however specific treatment may be needed for – Hypercalcemia: Bisphosphonate and inappropriate antidiuretic hormone secretion (fluid restriction and demeclocycline.

13. PULMONARY OEDEMA

The term pulmonary oedema may be regarded as an increase in the fluid content of the extravascular tissues of the lung. Table 52 enlists the causes of pulmonary oedema.

Table 52: Causes of pulmonary oedema

Cardiogenic –
• LV failure
• Myocardial infarction
• Mitral stenosis
• Cardiac arrhythmias
• LA myxoma
• Hypertensive encephalopathy
• Pulmonary infarction
Non-cardiogenic –
• Fluid overload (overhydration)
• Neurogenic – Fracture skull, encephalitis, post-ictal state, increased intracranial pressure
• Near-drowning
• Shock
• Infections – Endotoxins from gram-negative septicaemia, pneumonia and bronchopneumonia
• Inhalation of noxious fumes and gases – Nitrogen dioxide, chlorine, hydrogen sulphide, sulphur dioxide, ammonia, phosgene, mustard gas, ozone, paraquat, polymer fumes, certain metallic salts
• Inhalation of gastric acid (Mendelson's syndrome)
• Rapid aspiration of large pleural effusion
• High altitude pulmonary oedema
• Uraemia
• Trauma – Capillary damage causing 'leaky lung'
• Toxic
a. Drug-induced: IV narcotic abuse particularly heroin, methadone, salicylates, propoxyphene. Cytotoxic drugs such as busulphan, bleomycin, cyclophosphamide. Nitrofurantoin.
b. Poisoning – Alcohol, organophosphorus, barbiturates
• Hypersensitive response – Blood transfusion (may also be due to fluid overload), angioedema, SLE, Goodpasture's syndrome

CLINICAL FEATURES

1. Onset – Sudden.
2. Feeling of oppression in chest.
3. Acute and distressing dyspnoea.
4. Incessant short cough and copious frothy, sometimes blood tinged fluid from mouth and nose. Phenomena of "cough, cough, cough – spit, spit, spit".
5. Sweats.
6. Feeble pulse.
7. Bubbling rales first at base, then over entire chest, Other physical signs relating to the cause of oedema e.g. septicaemia.
8. Fall of temperature.
9. Termination – may be fatal in few hours, the moist sounds increasing and becoming audible at a distance (death rattle), or symptoms may persist for 12–24 hours and disappear.

X-ray – "Bats wing" appearance of confluent shadows extending from hilar region into midzones. A radiological feature of pulmonary oedema fluid is that it shifts with gravity into the bases when patient is upright or to dependent lung if patient is on his side.

MANAGEMENT

(1) For treatment of acute left ventricular failure (Refer). (2) For oedema due to defective pulmonary drainage, e.g. chronic disease, coma, overdosage of drugs – (a) Maintenance of airway. (b) Tracheobronchial suction through catheter. (c) Bronchoscopy or tracheostomy and drainage.

(d) Administration of oxygen under pressure by mechanical assistance. (3) For circulatory overload – IV frusemide. (4) For high-altitude pulmonary oedema – Descent to lower altitude with supportive measures such as fluid replacement and ventilatory assistance. (5) Corticosteroids – in high doses for pneumonia, septicaemia and Mendelson's syndrome. (6) Treatment of specific cause if identified, e.g. emergency mitral valvotomy, control of systemic hypertension, treatment of septicaemia, etc.

14. PULMONARY THROMBOEMBOLISM

Pulmonary thromboembolism (PTE) is usually following venous thrombosis audes due to various predispoisng factors (Table 53).

CLINICAL FEATURES

I. Acute minor PE – due to obstruction of small distal pulmonary arteries resulting in lung infarction. Symptoms if they occur are tachypnoea, pleuritic chest pain and haemoptysis. No signs, or tachycardia, pleural rub and pyrexia. *Management*– Analgesia, oxygen and Heparin 100 IU/kg as loading dose, followed by infusion of 1000–2000 IU/hr. Oral warfarin started simultaneously. When warfarin is started during active thrombosis, levels of protein C and protein S fall, creating a thrombogenic potential. Oral loading of warfarin should therefore be covered by simultaneous IV heparin for 4–5 days. Oral anticoagulation is given to achieve an international normalized ratio (INR) of 2.0–3.0 and is usually continued for 3–6 months.

II. Acute major PE – follows significant obstruction to proximal pulmonary arteries.

1. SOURCE OF CLOT – (a) *DVT* – of veins of calves or pelvis. (b) *Heart* – Myocardial infarction, mitral stenosis, infective endocarditis, isolated myocarditis.
2. PRECIPITATING FACTORS – Straining at stool, out of bed or wheel chair, or paroxysm of cough.

Symptoms

1. *Circulatory collapse* – due to sudden reduction in cerebral and coronary blood flow from obstruction to RV outflow.
2. *Dyspnoea* – of sudden onset. Tachypnoea and hyperventilation. Asthmatic breathing if reflex bronchospasm.
3. *Chest pain* – (a) In precordium or retrosternal like angina or cardiac infarction. (b) Pain due to pleurisy may appear after few hours or days. Pain is usually worse on deep inspiration.

Table 53: Predisposing conditions for venous thrombosis

Common
• Major trauma
• Recent surgery
• Obesity and immobility
• Smoking
• Increasing age
• Oral contraceptive pill
• Malignant disease
Uncommon
• Hyperviscosity syndrome
• Nephrotic syndrome
• Underlying primary clotting abnormality e.g. defective fibrinolysis, elevated levels of antiphospholipid antibodies
• Congenital deficiencies of antithrombin III, protein C, protein S or plasminogen
• Factor V Leiden mutation

4. *Haemoptysis* – may occur.
5. *Syncope or death* – may occur when degree of pulmonary arterial obstruction is sudden and severe.

Signs

1. *Due* to *diminished cardiac output* – Sinus tachycardia. Hypotension, shock, impaired concentration, low urine output.
2. *Due to pulmonary hypertension and right ventricular failure* – Raised JVP, hepatic enlargement, diastolic gallop to left of midsternum. Pulmonic component of 2nd sound accentuated. Systolic murmur may appear in pulmonary area, it may have a scratchy quality suggesting pericardial friction rub. Systolic murmur may appear along left sternal border due to functional tricuspid regurgitation from right ventricular dilatation. Sometimes arrhythmias.
3. *Due to disturbance of pulmonary ventilation and perfusion* – Central cyanosis.
4. *Due to pulmonary infarction* – Usually after 12–24 hours. Fever, pleural rub, signs of consolidation. Effusion may develop, usually haemorrhagic.

INVESTIGATIONS

1. **ECG**– abnormal in about 25%. S_1, Q_3, T_3 pattern, RBBB, P pulmonale and right axis deviation.
2. **Chest radiography:**
   a. Dilatation of major proximal artery (right descending pulmonary artery Palla's sign) and areas of pulmonary focal oligaemia if major arterial obstruction - (Westermark's sign).

b. Wedge-shaped opacities in peripheral lung fields due to pulmonary infarction with or without small effusion may occur with minor PE - (Hampton's hump) (Fig. 37).

c. In chronic thromboembolic pulmonary hypertension, cardiothoracic ratio may be increased and may be evidence of RV dilatation. Patchy oligaemia and dilatation of main pulmonary arteries.

3. **Isotope radionuclide ventilation-perfusion** (V/Q) lung scanning– Normal perfusion scan rules out PE. When assessment of ventilation is made simultaneously, evidence of V/Q mismatch greatly increases likelihood of PE being the cause of reduced perfusion.
4. **Pulmonary angiography**– is indicated when the index of clinical suspicion is moderate or high, and isotope scan is equivocal.
5. **CT and MRI scanning**– can detect PE. Diagnostic criteria include constant intraluminal filling defects in several films and sharp cut off in vessels greater than 2.5 mm in diameter.

CT scan with intravenous contrast is investigation of choice as of now. Multi detector CT scan provides images better than conventional pulmonary angiography.

1. **D-dimer**– Increased levels in PE but not specific since elevated levels also occur postoperatively (for one week), in myocardial infarction, sepsis and other systemic illness.

   It is used for screening of suspected patients of pulmonary embolism.
2. **Venography and impedance plethysmography**– for testing for DVT.
3. 2D-echocardiography: it helps to rule out other conditions that mimic thromboembolism like pericardial tamponade, aortic dissection. In patients of PE, it shows hypokinesis of right ventricular free wall with normal movement of right ventricular apex – McConnell's sign.

MANAGEMENT

1. ***Relief of pain and apprehension*** – Analgesics
2. ***Oxygen***– to relieve hypoxia.
3. ***Thrombolysis***– Streptokinase loading dose of 250,000–600,000 IU is given over 30-minute period. Following this, a constant IV infusion of 1000,000 units/hour for upto 72 hours, or tPA 10 mg bolus, 50 mg over first hour, 20 mg over each hour for 2h. or Tenectaplase Thrombin time should be maintained at 1.5–2 times the control value. After a delay of 4 hours after stopping thrombolytic agent, heparin should be started.

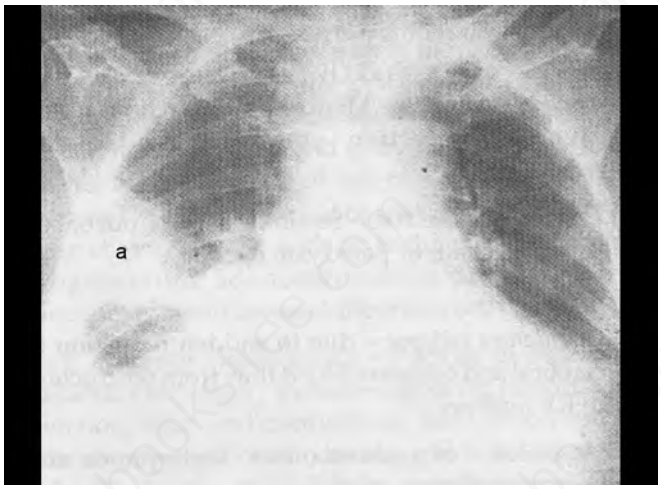


Fig. 37: Infarction of the lateral segment of the right middle lobe (a)

(Recombinant tPA 100 mg is given as continuous peripheral infusion over 2 hour)

4. ***Anticoagulants***– (a) *Heparin* – Loading dose of 10,000 units, followed by constant IV infusion at rate of about 1200 units/hour for 7–10 days. Dose is regulated by frequent measurement of APTT which should be maintained between at 1.5–2.5 times the normal. When higher doses are required of unfractionated heparin in those with DVT and FE, monitoring of plasma protein level is advisable. Low molecular weight heparins are less prone to binding than high molecular weight heparins, and therefore resistance is unlikely. Dose -2500 IU s.c. once daily. (b) *Warfarin* – 10 mg/day started after 7 days of IV heparin. Both drugs should be administered together for at least 4–5 days. Dose of Warfarin is adjusted to maintain PT at 1.5–2.5 times the normal value. The drug should be continued for 3 months. Persisting risk factors or a history of recurrent thromboembolism are indications for indefinite continuation of treatment.
5. ***Antibiotics***– to prevent secondary infection.
6. ***Vasopressor drugs, IV colloids***– for shock.
7. ***Pulmonary embolectomy***–

Indications

- Patient with massive embolism who shows evidence of deterioration after initial improvement.
- Failure of conservative measures to help a seriously ill patient within one hour. Cardiopulmonary bypass has been advocated to support the severely decompensated patient while immediate thrombolytic therapy or embolectomy is instituted.

Acute massive pulmonary embolism can sometimes be successfully disrupted using a catheter inserted into the pulmonary artery. The clot may be partially fragmented and improve pulmonary blood flow, and the smaller fragments may then respond more rapidly to thrombolysis.

PREVENTION OF FURTHER EMBOLIZATION –

1. *General measures* – Elevation of legs in order to collapse the veins. Use of elastic stockings. Leg exercises in the form of pressing the feet against the foot of the bed several times a day.
2. *Anticoagulants.*
3. *Inferior vena cava interruption* – with percutaneous insertion of devices such as filters and umbrellas. Indications—(a) Embolization in patients receiving anticoagulants. (b) Anticoagulants are contraindicated. (c) Diseases predisposing to venous thrombosis and pulmonary embolism are prominent and persistent. (d) Septic embolism.

III. Chronic thromboembolic pulmonary hypertension (CTEPH) – is rare and is a result of chronically increasing pulmonary arterial obstruction, caused by unresolved or recurrent emboli, or thrombosis *in situ*. It usually presents with gradual onset of dyspnoea with or without history of venous thrombosis or pulmonary emboli. Exertional chest discomfort may occur and clinical signs are those of RV pressure overload.

Management – Domiciliary oxygen for symptomatic relief. CTEPH is the only type of pulmonary hypertension that can be successfully treated with conservative surgery that is pulmonary thromboembolectomy (PTE). Inserting an IVF filter prevents further pulmonary embolism.

15. FUNGAL INFECTIONS OF THE LUNG

PREDISPOSING CAUSES

Usually opportunist infection due to:

- States of general debility such as malnutrition, diabetes mellitus, cachexia of malignant disease, blood dyscrasias, and lymphomas.
- Local damage to respiratory tract due to previous inflammatory, neoplastic, allergic or vascular disease.
- Iatrogenic:

  Antibiotics, especially broad spectrum such as tetracyclines.
  - Corticosteroids.
  - Cytotoxic and antileukaemic drugs.
  - Immunosuppressive drugs used, for example in transplant surgery.

CLASSIFICATION

1. ***Diseases due to actinomycetes***
   a. ***Actinomycosis*** – Pulmonary variety usually results from inhalation of the organism, but the lungs may also be infected via blood stream or by spread through diaphragm via abdomen. It produces chronic suppurative and granulomatous disease of one or both lungs, usually lower lobes. Pleura may be involved with resultant empyema. Abscess and sinuses may form on chest wall. *X-ray* – Irregular areas of consolidation and erosion of ribs. Sputum shows sulphur granules and culture will grow typical colonies. *Treatment* – Benzyl penicillin 2 mega units 8-hourly for 6 weeks, followed by 600,000 units or twice daily together with oral penicillin for 6 weeks. If sensitivity tests demand, streptomycin, or tetracycline or sulphonamide may be added.
   b. ***Nocardiosis*** – caused by Nocardia asteroids. May develop in agricultural workers. Disease pattern resembles that of tuberculosis but it tends to be more acute, lung abscesses may form, and infection may involve the brain. *Treatment* – Same as actinomycosis, the organism also responds to sulphonamides.
2. ***Diseases due to yeast and yeast-like fungi***
   a. ***Moniliasis*** – due to Candida albicans. A condition similar to thrush may occur in the bronchi resulting in irritating cough. Rarely moniliasis may invade the lung producing acute illness. Chest radiographs show ill-defined opacities in upper lobe, and occasionally septicaemia with endocarditis or meningitis results. *Management* – Removal of iatrogenic cause such as tetracycline. Pot. iodide by mouth. In severe infections Amphotericin-B.
   b. ***Torulosis*** – caused by Cryptococcus neoformans. If inhaled, it sets up a primary pulmonary lesion, usually minimal, but it may spread in the lung, producing a granulomatous consolidation resembling a tumour (toruloma), and may also cavitate. Lymphomas such as Hodgkin's disease often predispose to this condition. Diagnosis is by sputum mycology and by biopsy of bronchus or lung. *Treatment* – If a chronic lesion persists, surgical excision covered by fungicide therapy with Amphotericin-B or Hydroxystilbamidine.
3. **Diseases due to filamentous fungi**
   a. ***Aspergillosis*** – Aspergillus fumigatus is of chief importance, and agricultural workers are at special risk. The fungus may infect a lung previously

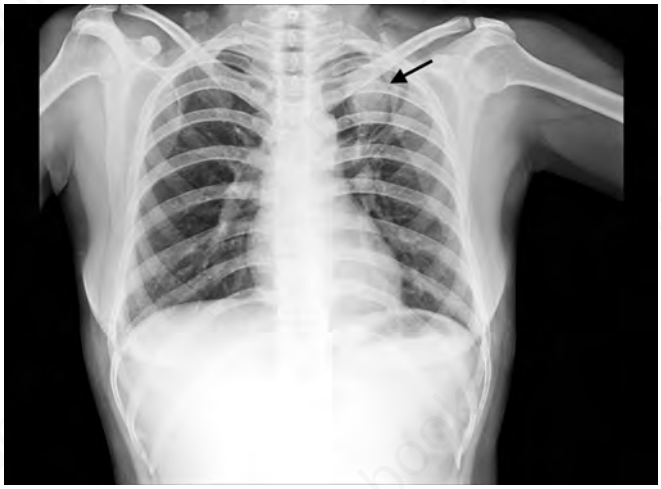


Fig. 38: Fungal ball in left upper lobe cavity

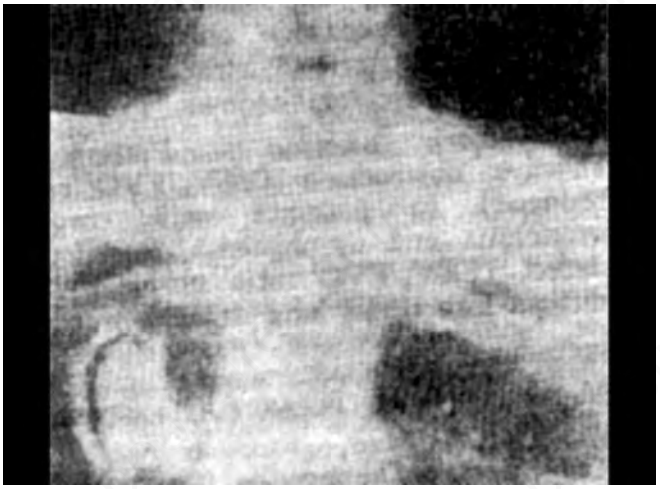


Fig. 39: Aspergilloma at right apex. The air space between the mycelial ball and the wall of the cavity is seen as a typical hypertranslusent crescent

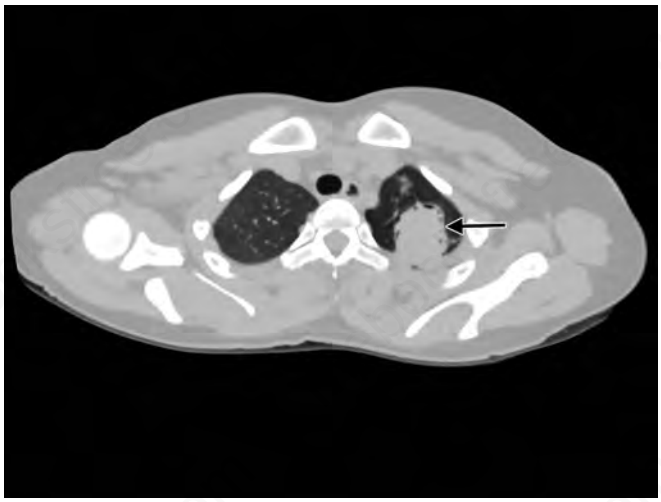


Fig. 40: HRCT chest showing fungal ball in supine position

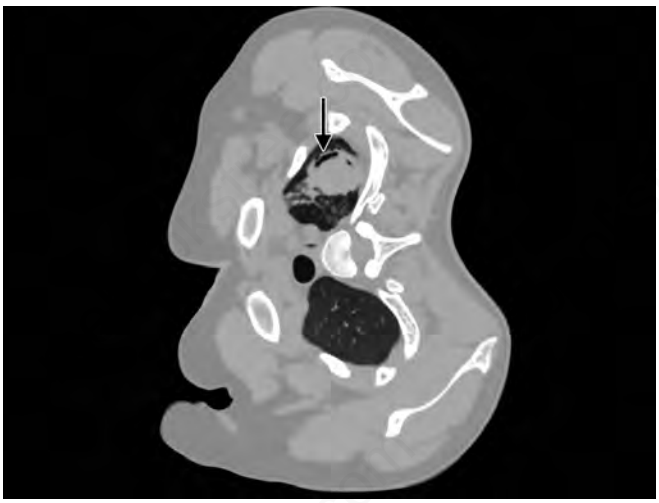


Fig. 41: HRCT chest of patient in Figure 40 in lateral decubitus showing change in position of fungal ball

damaged by a tuberculous cavity, unresolved pneumonia, pulmonary infarct or bronchiectasis. Three types of bronchopulmonary aspergillosis are known -

i. **Allergic bronchopulmonary aspergillosis** (ABPA)—In individuals with atopic hypersensitivity, high titres of IgE antibody and precipitating IgG antibody to *Aspergillus fumigatus* results in episodes of intense, usually focal inflammation of medium-sized bronchi. See Table 49 for criteria for the diagnosis of ABPA.

ii. **Aspergilloma** *(Mycetoma)* – Cavities from previous tuberculosis or sarcoid disease may become colonized by A. fumigatus. A ball-like fungal mass mixed with inflammatory debris and blood forms in the cavity, which becomes lined with highly vascular granulation tissue (Fig. 38). Typical symptom is recurring mild episodes of haemoptysis, but severe bleeding can occur. The fungal ball may be difficult to see on a plain radiograph (Fig. 39) but can be easily visualized on CT scan, crescent of surrounding air within lung cavity. High titres of Aspergillus precipitins are usually present (Figs 40 and 41). Treatment – Lobectomy for patients with severe haemoptysis. Endoscopic percutaneous intracavitary instillation of amphotericin or ketoconazole can be useful for high-risk patients for pulmonary resection.

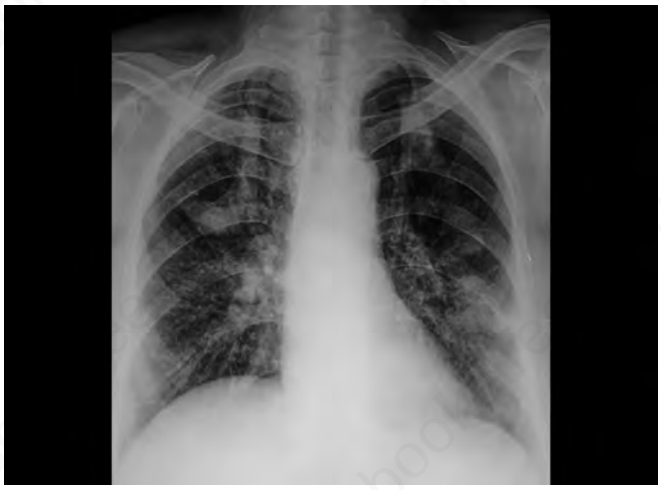


Fig. 42: X-ray chest showing gloved finger opacities and nodular infiltrates in both lung fields

iii. **Invasive aspergillosis**– In immuno-compromised individuals with severe neutropenia or T lymphocyte deficiency, invasive aspergillus infection of the lung parenchyma can produce an acute or subacute illness with fever and a local cavitary pneumonia or disseminated pneumonia. Diagnosis can be confirmed by demonstration of fungal hyphae in bronchoscopic or open lung samplings.

Voriconazole is preferred agent for invasive aspergillosis.

Stages of ABPA

Stage I - Acute: Patients are diagnosed with ABPA after meeting the diagnostic criteria mentioned above. Radiologically infiltrates in upper and lower lobes may be seen, good response to oral corticosteroids.

Stage II - Remission: Resolution of stage I findings for 6 months or longer when patients are off corticosteroids, chest X-ray may show complete resolution of infiltrates.

Stage III - Exacerbation: Relapse of symptoms, new infiltrates on chest radiograph, rising IgE levels.

Stage IV – End-stage: Patients whose diagnosis was missed in early stage and had received treatment for only asthma may progress to bronchiectasis, cavitatory changes and fibrosis.

Criteria for ABPA Diagnosis in Cystic Fibrotic Patients

1. Clinical deterioration (coughing, wheezing, increased sputum production, exercise intolerance and decrease in pulmonary function).
2. Immediate hypersensitivity to *A. fumigatus* (positive skin test or IgE response).
3. Total serum IgE concentration >1000 ng/mL.
4. Precipitating antibodies to *A. fumigatus.*
5. Abnormal chest X-ray (infiltrate, mucus plugs or unexplained changes compared to previous chest X-ray). **(Fig. 42)**.

TREATMENT

1. ***Oral corticosteroids*** - are the most effective treatment for acute phase of ABPA as they suppress the immunologic reaction and the inflammatory response. Dose: Prednisolone 0.5 mg/kg/day for 2 weeks, followed by progressive decrease in dose after 6–8 weeks. Treatments monitored by assessing symptoms are chest X-ray or CRST scan. Stage IV patients have severe asthma and in these cases, the minimal dose required to stabilise the patient must be identified.
2. ***Antifungal agents*** - Antifungal agent Itraconazole 200 mg/day for 16 weeks prevents disease progression in corticosteroid dependent ABPA patients without any toxic effect and can be used as an adjunctive therapy. Fibreoptic bronchoscopy may be necessary to remove the mucoid impaction responsible for atelectasis in rare cases.
3. ***Bronchial hygiene*** to improve airway clearance and inhaled bronchodilators to reduce bronchospasm. Pneumococcal vaccine and annual influenza vaccination should be included in management.

   b. ***Phycomycosis*** (Mucormycosis) – Inhalation of the spore produces an acute pulmonary infection often associated with infarction which may take the form of acute pneumonitis with cavitation. *Treatment* – Amphotericin-B and surgical excision of any chronic localised lesion.
4. **Diseases due to dimorphic fungi:**

   a. ***Histoplasmosis*** – caused by Histoplasma capsulatum. Primary lesions often calcify and produce hilar and miliary calcifications which are spherical and may show small air-space haloes. A secondary stage of more progressive disease produces fever, and emaciation with visceral involvement. It may mimic tuberculosis or produce tumour-like masses (Histoplasmoma). Enlarged lymph nodes may cause compressive symptoms due to involvement of vessels, airways or esophagus. Diagnosis depends upon positive culture. Serological tests show specific complement fixing antibody. *Treatment* – Amphotericin for several weeks.

   b. ***Coccidioidomycosis*** – *Coccidioides immitis* is a soil fungus. Acute and chronic clinical forms of the disease mimic histoplasmosis and meningitis.

Diabetics and immunosuppressed patients suffer more progressive disease and need amphotericin therapy. Diagnosis is by culture of organisms or microscopy of tissue sections. *Treatment* – Amphotericin.

c. ***Blastomycosis*** – due to Blastomyces dermatitides causes granulomatous and suppurative lesions presenting as subacute or chronic pulmonary infection. Infection mimics pulmonary tuberculosis and is often accompanied by dissemination to skin of face and arms, causing nodules and plaques. Chest X-rays show massive areas of consolidation. Often fatal but may respond to Amphotericin-B or Hydroxystilbamidine.

d. ***Sporotrichosis*** – caused by Sporotrichum schenckii occurs in farmers, nurserymen or woodmen. Usually affects skin first, and the disease may then spread to involve the lungs, or primary pulmonary infection which may become chronic. X-rays – Enlarged hilar shadows, miliary mottling and thin-walled cavities. Diagnosis by specific skin test and finding precipitating antibody in serum. *Treatment* – Potassium iodide. Other fungicides may be necessary.

16. AIRWAY PROBLEMS IN CHILDREN

CHRONIC UPPER AIRWAY OBSTRUCTION

1. *Laryngomalacia* is a relatively common condition presenting with variable inspiratory stridor in first few weeks of life. The immature laryngeal cartilages are soft, and supraglottic, collapse particularly of the arytenoids and epiglottis, occurs during inspiration. In most cases, the infant is noisy, but there is minimal respiratory distress. The stridor tends to settle during the first 2 years of life but may transiently worsen with intercurrent viral infections.
2. *Subglottic stenosis* may be congenital or acquired, the latter being an important cause of stridor in infants who were born preterm, as a consequence of scarring from intubation. There is often repeated history of 'croup' that may be slow to resolve. Children with moderate to severe stenosis have biphasic stridor. Treatment depends on severity of stenosis. Severe cases require tracheostomy and laryngotracheal reconstruction.
3. *Airway haemangiomas* are uncommon. They enlarge during first few months of life and present with stridor. The larynx is the common site and 50% of children have cutaneous haemangiomas. Tracheostomy is required until spontaneous involution of the haemangioma is complete (usually by age of 5 years).
4. *Vocal cord palsy* – Vocal cord palsies are uncommon and present with stridor. Tracheostomy is necessary for bilateral palsy. Damage to recurrent laryngeal is the most common cause of unilateral palsy.

ACUTE LOWER AIRWAY OBSTRUCTION

1. ***Bronchiolitis:*** Respiratory syncytial virus (RVS) is responsible for majority of cases. Classical features are tachypnoea, chest wall recession and hyperinflation, crepitations and wheeze are heard on auscultation. Diagnosis is confirmed by examination of nasolaryngeal aspirates for viral immunofluorescence.

   Bronchiolitis obliterans is rare complication of bronchiolitis resulting in fibrosis and permanent damage to lower airways. Prognosis is variable, some children develop progressive respiratory failure.
2. ***Bronchial foreign body:*** A bronchial foreign body must be considered in toddlers and young children presenting with acute wheeze of sudden onset. There may or may not be a recent history of choking. The foreign body may enter right or left main stem bronchus. Ball valve obstruction with over inflation.

   Distal impaction may result in lobar collapse.

CHRONIC LOWER AIRWAY OBSTRUCTION

1. ***Bronchiectasis*** is uncommon in children. Causes –
   - Cystic fibrosis
   - Primary ciliary dysplasia (including Kartagener's syn.)
   - Immunodeficiency
   - Post-infectious adenovirus, *Bordetella,* undetected foreign body
   - Aspiration (e.g. H-type fistula, GER, swallowing incoordination (with neuromuscular problems)
   - Antitrypsin deficiency
   - Idiopathic
2. ***Bronchopulmonary dysplasia*** affects about 25% of all children before 28 weeks generation. Initial respiratory failure associated with hyaline membrane disease, trauma from ventilation (volutrauma) and oxygen toxicity contributes to the airway and parenchymal lung damage. Intercurrent infections are common.
3. ***Tracheomalacia*** occurs almost exclusively in infants. The tracheal cartilages are soft and have a tendency to collapse. Symptoms vary from mild, with intermittent expiratory stridor, to severe, with episodes of apnoea and cyanosis termed 'death spells', that are usually associated with feeding. Ventral suspension of trachea by aortopexy in severe cases.

Table 54: Stages of sarcoidosis	
Stage 0	Clear chest X-ray
Stage 1	Bilateral hilar/ mediastinal adenopathy
Stage 2	Bilateral hilar adenopathy and pulmonary infiltration
Stage 3	Bilateral infiltration without hilar adenopathy
Stage 4	Pulmonary fibrosis involving the upper lobes, traction bronchiectasis is common

17. PULMONARY SARCOIDOSIS

Sarcoidosis is a granulomatous inflammatory disorder of unknown cause. It principally affects young adults and has a variable presentation and course. Although sarcoidosis may affect any organ of the body, the mediastinal lymph nodes and lungs are affected in 90% of cases. See Table 54 for the stages of sarcoidosis.

AETIOLOGY

Genetic influences: There are reports of familial clustering in disparate ethnic groups, and evidence of a strong relationship between sarcoidosis and MHC class II alleles on chromosome 6. It is likely that genetic influences will be found that affect susceptibility to the disease, mode of presentation (acute or chronic) and responsiveness to corticosteroids.

PATHOLOGY AND PATHOGENESIS

Granulomas are the classical lesions and may be distributed in multiple organ systems including the lymph glands, lungs, liver and spleen. Analysis of BAL fluid in acute onset sarcoidosis shows intense concentration of activated $CD4^+$ lymphocytes (helper cells) with release of inflammatory mediators (cytokines) and interferon-α. Why this immune-mediated response 'switches off' in some but persists and progresses to fibrosis in others remains unexplained.

CLINICAL FEATURES

1. *Onset* - Sarcoidosis may present acutely (Lofgren syn.), in subacute manner or insidiously. About half the patients are asymptomatic and sarcoidosis is commonly detected by chest radiograph.
2. *Symptoms* - Consist of unproductive cough and shortness of breath.
3. *Systemic manifestations* - (a) CNS - Neurosarcoidosis may manifest as paralysis of the nerves at the base of the brain, spine and of peripheral nerves. (b) Liver - Enlargement with elevated liver enzymes. (c) Heart - Brady or tachycardia, dysrhythmias, cardiomyopathy. (d) Skin - macules, nodules and plaques on nose, cheeks, lips and ears. Erythema nodosum in Lofgren syn. (e) Uveo-parotid fever (Heerfordt syn.). Parotitis with facial nerve palsy and eye symptoms. (f) Joints - Main manifestation in Lofgren syn. (i) Arthralgia, often accompanied by erythema nodosum and an enlarged hilum. (ii) Intermittent monoarticular or polyarticular arthritis or persistent.

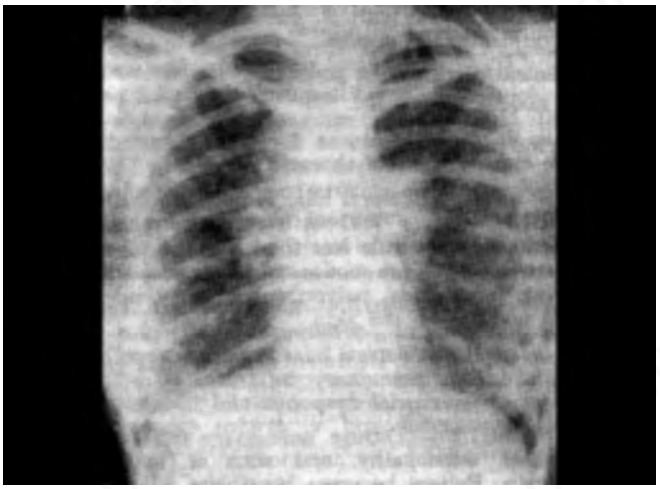


Fig. 43: Enlarged hilar and paratracheal lymphnodes in sarcoidosis

DIAGNOSIS

1. ***Chest radiograph*** – Bilateral hilar adenopathy (Fig. 43).
2. ***CT scan*** - Bilaterally enlarged hilar and mediastinal lymphnodes, thickening and nodules along the bronchovascular bundle, small nodules located in upper lobes and along the pleura, and interlobular septa.
3. ***Tissue biopsy and histology*** - Transbronchial lung biopsy in combination with biopsies of bronchial mucosa, reveals non-caseating granuloma even in patients with radiographic normal lung parenchyma. If no conclusive results, surgical biopsies by mediastinoscopy or thoracoscopy may be necessary.
4. ***Non-invasive tests*** - (a) *Bronchoalveolar lavage.* BAL fluid shows increase in T lymphocytes. (b) *Gallium scintigraphy* may show tracer accumulation in mediastinal lymph nodes along with an uptake in the parotid glands. (c) *Mantoux test* may be positive in chronic forms, but may be negative in active sarcoidosis. (d) *Angiotensin converting enzymes (ACE)* level is neither specific nor sensitive.

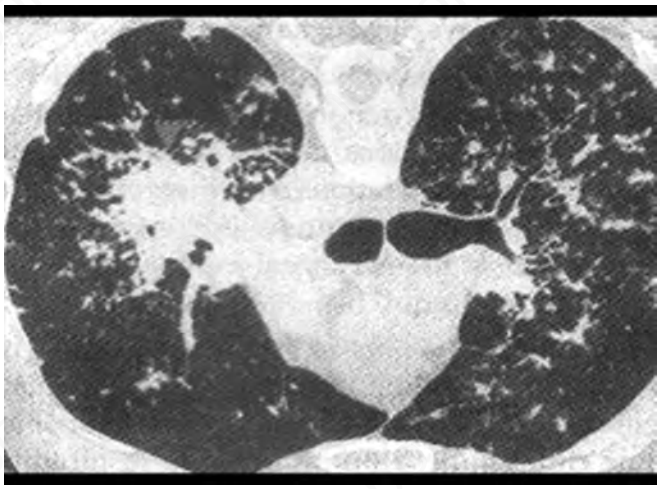


Fig. 44: HRCT of the lungs showing peribronchovascular nodules causing a 'beading' appearance with hilar lymphadenopathy

Table 55: Extra (-) pulmonary manifestations of sarcoidosis

• Skin	Erythema nodosum, lupus pernio, infiltrates, pruritus
• Eye	Uveitis, retinitis, glaucoma, sicca syndrome
• CNS	Bell's palsy, lymphocytic meningitis
• Liver/spleen	Raised enzymes, hepatosplenomegaly, portal hypertension
• CVS	Cardiomyopathy, heart block, arrhythmias, SVC obstruction
• Glands	Diffuse adenopathy - parotid, salivary, lachrymal
• Metabolic	Hypercalcemia, hypercalciuria, hypopituitary syndrome, hypo-thyroidism, tumour necrosis factor pyrexia syndrome
• Renal	Interstitial nephritis, nephrotic syndrome, nephrolithiasis
• Musculoskeletal	Cystic dactylitis, polyarthritis, myositis, nasal septum perforation.

TREATMENT

Stage I disease commonly resolves and does not need treatment unless presence of significant symptoms. Stage II and III disease with pulmonary and systemic involvement - (a) Prednisolone 20–40 mg/d × 4 wks followed by maintenance dose of 10 mg/d. (b) Immunosuppressant - Azathioprine or methotrexate as steroid sparing agents, if cannot be maintained on a low dose prednisolone. (c) Hydroxychloroquine for dermal, bone and joint involvement.

Lofgren's syndrome is an acute form of sarcoidosis characterized by erythema nodosum, bilateral hilar lymphadenopathy and polyarthralgia or polyarthritis.

Table 56: Causes of non-necrotizing pulmonary granulomas

Infections:
1. *Bacterial*
– M. Tuberculosis
– Non-tuberculous mycobacteria
2. *Fungal*
– Histoplasma
– Cryptococcus
– Blastomyces
– Pneumocystis
– Aspergillus
– Coccidioides
3. *Miscellaneous*
– Sarcoidosis
– Lymphoma
– Carcinoma
– Granulomatosis with polyangiitis
– Churg-Strauss syn.
– Brucellosis
– Crohn's disease
– Hypersensitive pneumonitis
– Berylliosis
– Talc granulomatosis
– Rheumatoid nodule
– Cat scratch disease
– Granulomatosis arteritides
– Hypogammaglobulinaemia.

HRCT of the lungs shows characteristic peribronchovascular nodules causing a 'beading' appearance with hilar lymphadenopathy (Fig. 44).

EXTRAPULMONARY SARCOIDOSIS

Table 55 lists the extra-pulmonary manifestations of sarcoidosis.

DIFFERENTIAL DIAGNOSIS

Causes of non-necrotizing pulmonary granulomas (Table 56) should be considered.

18. DIFFUSE PARENCHYMAL LUNG DISEASE

Diffuse parenchymal lung disease (DPLDs) represent a heterogenous group of principally inflammatory processes affecting the alveolar wall and often associated with exudates or transudates in the alveolar airspaces. Because

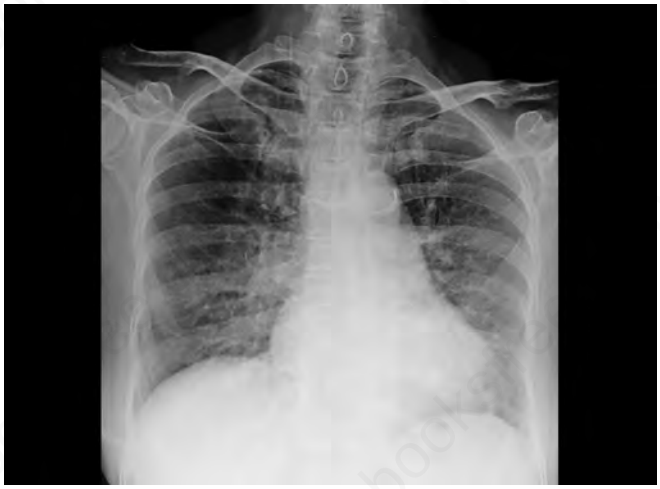


Fig. 45: X-ray chest suggestive of idiopathic pulmonary fibrosis

the disease affects the peripheral part of the lung, chest radiographs usually show widespread pulmonary shadows (Fig. 45). Causes are listed in Table 57.

Table 57: Causes of diffuse parenchymal lung disease

Cause known:
• Organic dusts (extrinsic allergic alveolitis)
• Inorganic dusts (pneumoconiosis)
• Gases or fumes
• Drugs or radiation
• Infection.
Cause unknown:
• Cryptogenic fibrosing alveolitis
• Interstitial lung disease associated with rheumatoid disease (e.g. RA and systemic sclerosis)
• Granulomatous diseases (Sarcoidosis, Langerhans cells histiocytosis)
• Neoplasia (e.g. lymphoproliferative disease, metastases, and lymphangitis carcinomatosa)
• Vasculitis
• Inherited diseases (e.g. neurofibromatosis, tuberous sclerosis)
• Miscellaneous (amyloidosis, alveolar proteinosis).

DIAGNOSIS

History

Occupation and pastimes– Domestic and occupational exposures to dusts, and relation and exposure to birds such as pigeons.

Family and other history– Family history in cystic fibrosis. Some congenital conditions (e.g. neurofibromatosis) are associated with DPLD. Smokers are less likely to have sarcoidosis or allergic alveolitis and more likely to have Langerhans cell histiocytosis or Goodpasture's syndrome. A careful drug history is necessary. Risk factors for HIV and other forms of immunodeficiency should be sought.

Respiratory symptoms – (a) Breathlessness is not episodic unless caused by extrinsic allergen. (b) Wheeze is a feature in pulmonary eosinophilia associated with asthma, or occasionally with LVF. (c) Cough is not of diagnostic help. Large volumes of sputum (bronchorrhea) occur occasionally in bronchoalveolar carcinoma, and a long history of purulent sputum suggests bronchiectasis. (d) Hemoptysis is common in pulmonary hemorrhage and vasculitis, but seldom occurs in chronic DPLD.

Systemic symptoms: (a) Fever suggests infection, but also occurs in vasculitis, drug-induced lung disease and malignancy. (b) Weight loss if significant indicates malignancy or miliary TB. (c) Arthralgia or arthritis favour connective tissue disease or systemic vasculitis.

Examination

(1) Clubbing is characteristic of FA and asbestosis, and seen occasionally in bronchiectasis. (2) Fine crackles (initially basal and inspiratory, later more widespread and expiratory as well) are hallmark of FA asbestosis. Crackles of bronchiectasis are coarser and occur in early inspiration; in extrinsic allergic alveolitis crackles often occur with a variety of squeaks.

Sarcoidosis reveals widespread radiographic shadowing but little abnormality on examination, whereas in FA patient may have a nearly normal chest radiograph, but profuse crackles.

Chest Radiography

Distribution of shadowing and size and shape of nodularity often give important diagnostic clues (Tables 58 and 59).

INVESTIGATIONS

Primary Investigations

Lung function tests – Most DPLDs cause restrictive defect with reduction in vital capacity, total lung capacity and carbon monoxide transfer factor.

Arterial blood gases – At rest both PaO_2 and $PaCO_2$ may be normal or reduced. Arterial desaturation on exercise may be early indication of DPLD.

Table 58: Diagnostic clues on chest radiography

	Basal	*Mid-zone*	*Upper zone*	*All zones*	*Peripheral*
Nodules/irregular shadows	CFA Asbestosis	Sarcoid	Chronic (fibrotic) sarcoid Silicosis	Miliary TB Coal worker's pneumoconiosis Metastases Tuberculosis EAA ARDS	
Confluent shadowing	Alveolar proteinosis	Pul. oedema *Pneumocystis jiroveci*			Pulmonary eosinophilia

Table 59: Causes of diffuse radiographic shadowing

	Acute	Chronic
Infection	Pneumonia (bacterial, viral, fungal)	Miliary TB
Hemodynamic	LVF, fluid overload	Chronic pulmonary venous hypertension
ARDS	Trauma, sepsis	
Allergic	Acute extrinsic allergic alveolitis	Chronic extrinsic allergic alveolitis (e.g. farmer's lung)
Pneumoconiosis		Asbestosis, silicosis
Drugs, toxins	Cytotoxics, inhalation of chlorine	Cytotoxics, amiodarone, radiotherapy
Hemorrhage/ vasculitis	Wegener's granulomatosis, Goodpasture's syndrome	
Malignancy		Lymphangitis carcinomatosis (Fig. 46), bronchoalveolar cell carcinoma
Suppurative lung disease		Bronchiectasis
Unknown cause		Sarcoidosis, fibrosing alveolitis, ± connective tissue disease, cryptogenic organizing pneumonitis, other rare diffuse parenchymal lung diseases

Blood tests – (a) Raised eosinophil count in pulmonary eosinophilia. (b) High titre of rheumatoid or antinuclear factors can suggest connective tissue disease. (c) Positive anti-neutrophil cytoplasmic antibody in Wegener's granulomatosis and related Vasculitides. (d) Positive serum precipitins (e.g. to avian or farmer's lung antigens), which are strongly suggestive of EAA.

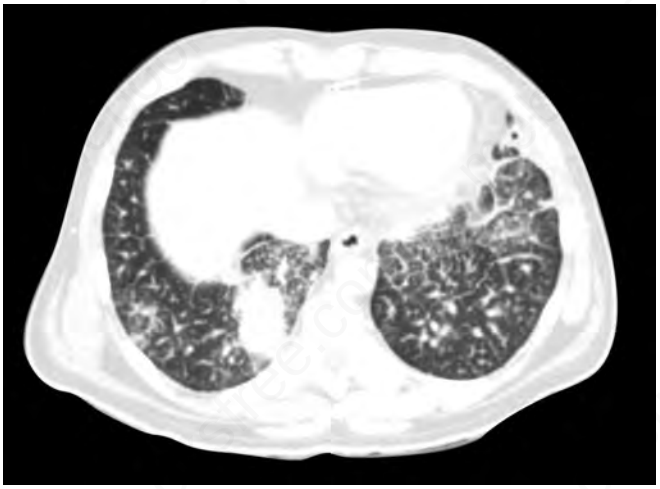


Fig. 46: HRCT chest showing lymphangitis carcinomatosis

FURTHER INVESTIGATIONS:

High resolution CT (HRCT) can be useful in suspected cases of CFA (reticular sub-pleural changes), asbestosis (detection of early changes) and lymphangitis (beading of interlobular septa, polygonal lines).

Lung biopsy – (a) Transbronchial – Sarcoidosis, tuberculosis, berylliosis, EAA, lymphangitis carcinomatosa. (b) Open lung or thoracoscopic (VATS) – FA, rheumatological disease, other diffuse fibrosing lung disease, video-assisted pulmonary vasculitis, lymphangio-leiomyomatosis, Langerhans cell histiocytosis.

Bronchoalveolar lavage– to sample cells and non-cellular material from lower respiratory tract. Lipoproteinaceous material (in alveolar proteinosis). Intracellular X bodies (in histiocytosis X). Hemosiderin macrophages indicate pulmonary hemorrhage, asbestos bodies in asbestosis. Predominantly lymphocytic lavage suggests sarcoidosis or EAA.

Scanning – Technetium - DTP scanning is a sensitive marker of lung inflammation; it may help to predict progress in fibrosing alveolitis.

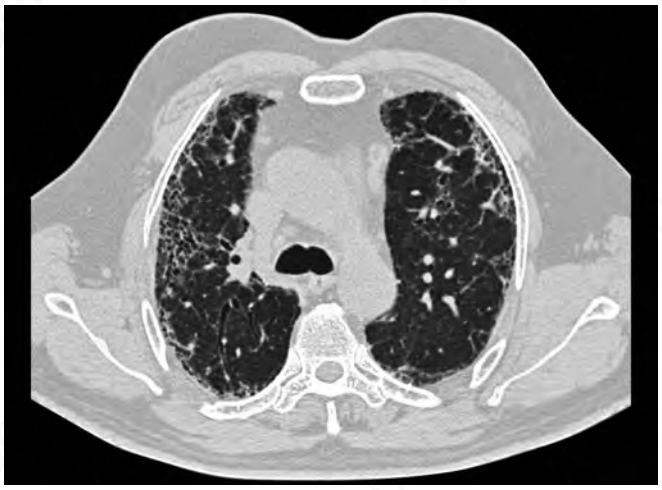


Fig. 47: HRCT chest showing interstitial lung disease UIP pattern

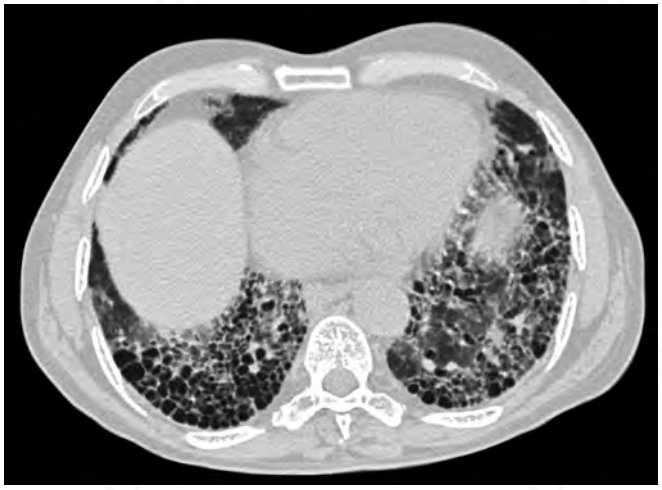


Fig. 48: HRCT chest showing interstitial lung disease UIP pattern honeycombing

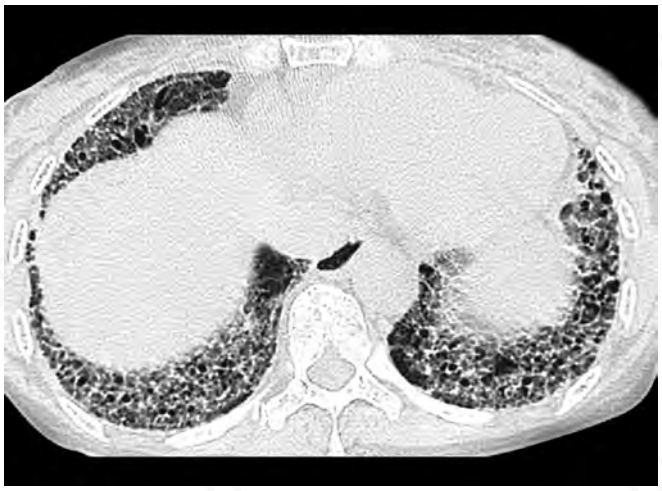


Fig. 49: Axial HRCT showing fibrotic pattern of NSIP in a patient with scleroderma, note the dilated esophagus

Cardiopulmonary exercise testing – Hypoxia may not be present at rest and induced by exercise which helps to uncover underlying lung disease. 6-minute walk test can be used for same; drop in oxygen saturation can be seen depending on distance after which drop is seen and degree of reduction in saturation gives information about underlying disease condition.

SPECIFIC DIFFUSE PARENCHYMAL LUNG DISEASES

Idiopathic interstitial pneumonias. Fibrosing alveolitis is a clinical syndrome based on bilateral interstitial shadowing on chest radiograph with bilateral, basal inspiratory crackles and restrictive lung function, that occurs alone (termed 'CFA' or idiopathic pulmonary fibrosis (IPF) or with connective tissue disorders (e.g. RA, systemic sclerosis). However, within this broad clinical syndrome, seven different histological patterns have been recognized, in what are now termed the 'idiopathic interstitial pneumonias' (IIPs). The HRCT appearance and prognosis of these entities differ. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the most common.

- UIP is characterized by areas of fibrosis with fibroblastic foci alternating with areas of normal lung. It is seen in diseases like asbestosis, sarcoidosis, chronic eosinophilic pneumonia, radiation injury (Figs 47 and 48).
- In NSIP, inflammation and fibrosis are uniform across the biopsy, with ground glass shadowing and linear opacities on CT. NSIP often occurs with RA, progressive systemic sclerosis and other connective tissue and collagen vascular diseases and has a better prognosis than UIP (Fig. 49).

CRYPTOGENIC FIBROSING ALVEOLITIS (IDIOPATHIC PULMONARY FIBROSIS)

Aetiology—CFA is caused by several different agents on a background of individual genetic predisposition. Exposure to metal or wood dust may be responsible for some cases. Previous antidepressant use may also be important. There is an association with an interleukin-1 receptor antagonist polymorphism, and genetic variation in transforming growth factor B may influence disease progression. There is a strong association with cigarette smoking.

Table 60: Common ILDs
1. Hypersensitivity pneumonitis
2. Sarcoidosis
3. Cystic lung disease such as lymphogranulomatosis and histiocytosis X
4. Associated with collagen vascular disease and connective tissue disorders
5. Idiopathic pulmonary fibrosis which has subtypes, including cryptogenic organizing pneumonia
6. Drug - induced
7. Occupational, as in silicosis

Clinical features—Most patients present with breathlessness, cough and arthralgia; occasionally after routine chest radiography, and 5% are asymptomatic. Clubbing and late inspiratory, mainly basal crackles are found. Expiratory crackles, cyanosis and cor pulmonale occur late.

Investigations – (a) Lung function tests usually show a restrictive defect with reduced gas transfer. (b) Chest radiography – Reticular or reticulonodular shadowing, predominantly over lower zone but extending to other zones. Lung size is reduced and honey combing may develop. (c) HRCT UIP: Patchy, predominantly peripheral and basal reticular and honeycomb changes with irregular septal thickening. NSIP: Ground-glass shadowing and absence of honeycombing. (d) Biopsy in those with unusual clinical features, when HRCT is not typical, and in young patients who may become eligible for transplantation. VATS biopsy is the preferred technique.

Management – (a) Oral corticosteroids improve lung function in about 25% and symptoms in about 50%. (b) Immunosuppression – Azathioprine in combination with prednisolone. Cyclophosphamide has been used in cases of systemic sclerosis, vasculitis, rheumatoid arthritis with variable success.

Interstitial lung diseases (ILDs) form a heterogenous group of disorders, characterised by predominant involvement of the interstitium. The alveolar spaces may also be concurrently involved. The common ILDs are listed in Table 60.

Diagnosis: *HRCT* of the lung allows extremely high-resolution image of the lung parenchyma. It is possible to pick up pathology in small structures such as the interlobular septae and secondary pulmonary nodules. HRCT of the lungs plays an integral role right from initial diagnosis, through characterization and finally monitoring of treatment in ILDs.

Table 61: Types of lung reaction
• Acute pulmonary oedema coming on within minutes or hours of exposure
• Acute tracheitis and bronchitis
• Destructive changes in lung parenchyma resulting ultimately in pulmonary emphysema and chronic airways obstruction
• Bronchial asthma
• Pulmonary fibrosis slowly progressing to cause restrictive disorder of lung function
• Malignant disease of lung or pleura after prolonged exposure

19. OCCUPATIONAL LUNG DISEASE

Occupational exposure to toxins and dusts produce various types of lung reactions (Table 61).

CLINICAL FEATURES

Depend on the Type of Inhalation

A. **Acute tracheobronchial or lung irritation**– e.g. gases such as ammonia, chlorine, fluorine, bromine, sulphur dioxide or nitrogen oxide. Metallic fumes or some metallic dusts, e.g. cadmium, zinc, magnesium. Symptoms of tightness of chest, hoarseness of voice, cough and wheezing, acute pulmonary oedema. Rarely acute chemical pneumonia.

B. **Pneumoconiosis**– Pulmonary disease resulting from inhalation of dust over sufficient length of time resulting in fibrosis of lung.

1. ***Due to inorganic dusts:***

i. SILICOSIS – caused by inhalation of free silica in quarrying and rock-drilling of quartz, flint and sandstone. Stages – (a) Bronchial with shortness of breath and exaggeration of linear markings on X-rays. (b) Nodular with discrete shadows in lung tending to coalesce seen in upper lobes (Fig. 50). Egg shell calcification of hilar nodes diagnostic. (c) Infective phase with fibrosis due to chronic tuberculous infection. Talc pneumoconiosis may be modified silicosis.

ii. COAL WORKER'S PNEUMOCONIOSIS (Anthracosis)—the (a) *Simple coal worker's pneumoconiosis* – diagnosed on basis of small rounded opacities fairly uniform in size. Not associated with any symptoms or impairment of lung function. (b) *Complicated coal worker's pneumoconiosis* is associated with progressive, predominantly upper lobe mass formation and fibrosis (progressive massive fibrosis, PMF). c) Caplan syndrome, first described in coal miners but subsequently in patients with silicosis, is the combination

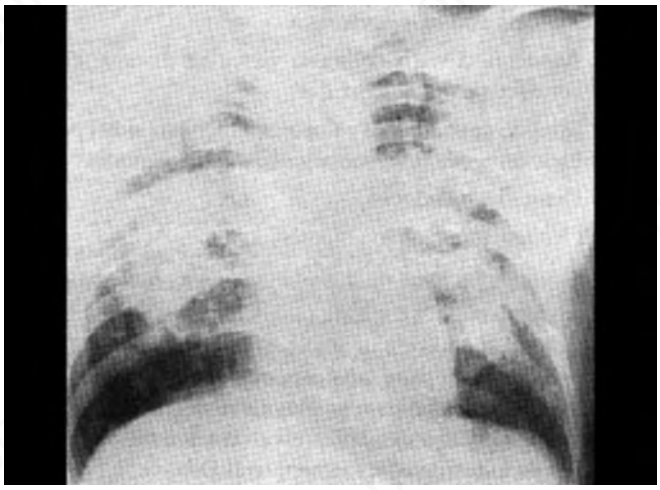


Fig. 50: Silicosis with massive conglomerate densities and basal emphysema

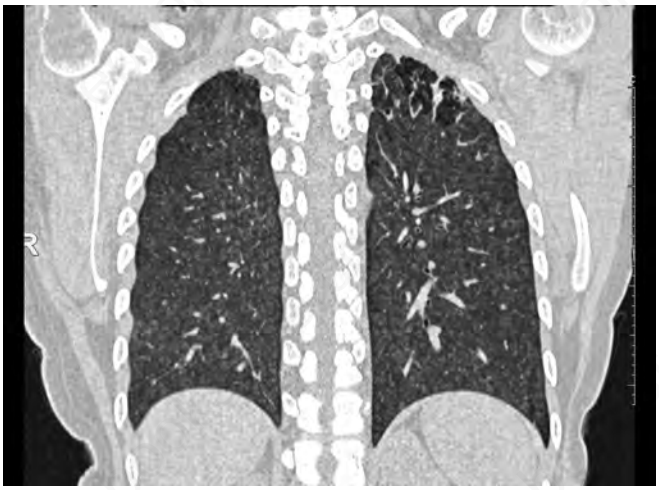


Fig. 51: HRCT chest showing hypersensitvity pneumonitis with ill-defined nodules

Table 62 Classification of EAA

Disease	*Source*	*Antigen*
Farmer's lung	Mould hay	Thermoactinomyces vulgaris
Bird fancier's lung	Avian droppings (mostly pigeons)	Avian protein in faeces, feathers
Mushroom worker's lung	Mushroom compost	Mushroom spores
Malt worker's lung	Mould barley	Aspergillus species
Bagassosis	Sugar cane dust	Thermophilic fungi Actinomycetes
Wood worker's lung	Wood dust	Wood dust
Isocyanate lung	Paints	Paints

of pneumoconiotic nodules and seropositive rheumatoid arthritis. Silica has immunoadjuvant properties and is often present in anthracitic coal dust.

iii. ASBESTOSIS – Fibrosis of lung due to inhaled asbestos dust. Besides asbestosis, asbestos produces pleural plaques, carcinoma of lung, malignant mesothelioma of pleura, pericardium and peritoneum; pleural effusion, diffuse pleural thickening and skin corns. X-ray shows presence of fine irregular linear opacities at lung bases.

iv. PNEUMOCONIOSIS – Due to metal inhalation – Iron (siderosis), beryllium (berylliosis), aluminium (aluminosis), tin (stannosis).

2. **Due to organic dusts:**

EXTRINSIC ALLERGIC ALVEOLITIS – is a diffuse alveolar, bronchiolar and interstitial disease that results from allergy to repairable environmental organic dusts. See Table 62 for the classification.

Symptoms – may be acute or chronic. (a) *Acute EAA* – Repeated episodes of an influenza-like illness with cough and shortness of breath, which begin from 1–10 hours after each exposure. Occasionally there is wheezing. Symptoms begin to subside within 12–24 hours. (b) *Chronic EAA* – is commonly seen with low but near-continuous exposure. There is slowly progressive loss of exercise tolerance due to breathlessness with or without accompanying cough. Main signs are inspiratory crackles and squeaks. Clubbing is rare.

OTHER AGENTS

Flock-worker's lung is an abnormal pulmonary response to inhaled nylon flock. During the flocking process, nylon-based fabric is cut finely to produce fabric used for upholstery.

Investigations – (a) Chest radiography – In acute EAA shows small (1–3 mm) nodules most common in lowest zones or diffuse infiltrates. In disease, upper and mid-zone fibrosis. (b) HRCT – patchy ground-glass shadowing and ill-defined nodules in acute EAA (Fig. 51). In chronic EAA fibrosis and irregular opacities. (c) Lung function tests – Restrictive lung function with reduced gas transfer. (d) Serum Precipitins: Assaying for precipitating IgG antibodies against specific antigens can be a useful adjunct in the diagnosis of HP.

Management: 1. *Preventive* – by controlling the dust at source. Symptomatic treatment, e.g. for exudative disease following exposure to gases or fumes – Rest and warmth, positive pressure oxygen with if necessary mechanical ventilatory assistance, correction of haemoconcentration in some cases, broad spectrum antibiotics if signs of infection, corticosteroids IV for few days followed by oral prednisolone, and sedatives in small doses to allay anxiety

or pain. 2. *Treatment of complications* – such as infections and cardiac failure.

20. LOBAR COLLAPSE OF THE LUNG

Collapse or atelectasis means airlessness or a loss of volume in the lung, lobe or segment from any cause. It may be obstructive due to occlusion of bronchus to the involved area, or may result from contraction due to chronic inflammation and fibrosis. In general usage the term *atelectasis* is confined to these two types of volume loss.

CAUSES

1. **Obstructive collapse** – (Resorption collapse) – occurs due to resorption of air distal to the bronchial obstruction and is of two types:
   a. ***Central obstructive collapse***– due to obstruction of major bronchus or collapse with bronchostenosis:

- *Within lumen* – (a) Plugs of mucus from bronchial secretions, mucus impaction caused by Aspergillus fumigatus. (b) Inhalation of foreign bodies, blood or mucopurulent secretions from upper respiratory passages.
- *Within the wall* – Adenoma or carcinoma of bronchus, stenosis.
- *Outside the bronchus* – Aneurysm, enlarged glands, neoplasm, inflammatory mass or reticulosis.

CLINICAL FEATURES

Loss of hemithorax volume with reduced breath sounds and voice sounds, due to obstruction of bronchial lumen.

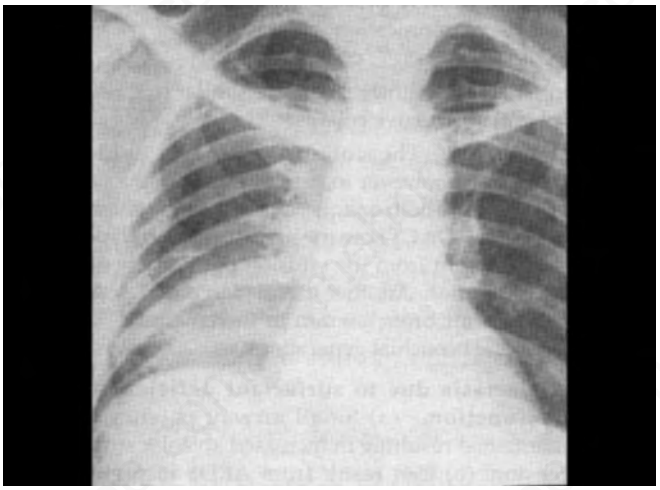


Fig. 52: Collapse of right lower lobe, preservation of outline of right heart border with elevated right hemidiaphragm

However in upper lobe collapse with shift of the trachea, the proximity of the collapsed upper lobe allows breath sounds and voice sounds to be conducted to the chest. Occasionally a monophonic or fixed wheeze is heard over the collapsed lung due to incomplete bronchial obstruction.

INVESTIGATIONS

Chest radiograph – (Figs 52 and 53)

- Displacement of the interlobar septa bounding the affected lobe; the degree of displacement varies with the extent of the collapse.
- Radiopacity of the affected lobe, reflecting the loss of aeration. In a collapsed lobe that still contains some air, the vascular markings may remain visible and the vessels may appear to lie close together.
- Secondary signs of lobar collapse – Unilateral elevation of the diaphragm, shift of mediastinal structures towards the side of affected lobe, ipsilateral decrease in size of thoracic cage, compensatory emphysema of the uninvolved lobes, and hilar displacement.

  CT scan – The obstructed and collapsed lung shows increased density obliterating normal blood vessels and mucous filled bronchi. After contrast injection the mucous filled bronchi do not enhance the mucous bronchogram.

  Bronchoscopy – is essential for management of collapse with major bronchial obstruction, for diagnosis and for therapy. Mucus impaction may require therapeutic bronchoscopy after chest physiotherapy has

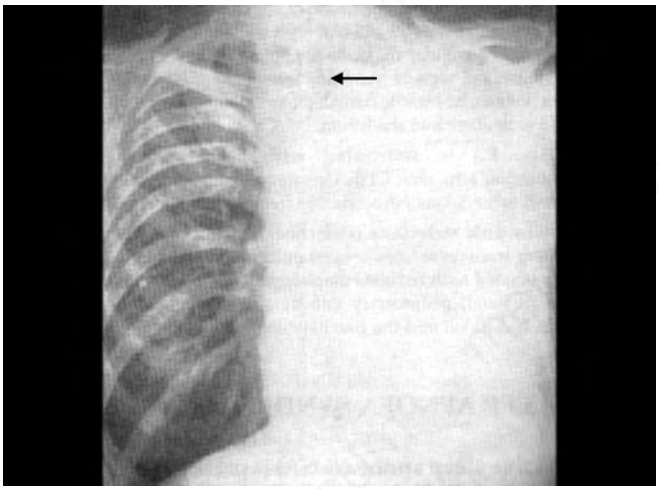


Fig. 53: Unilateral homogenous opacity obliterating practically whole of one lung field, due to massive collapse with mediastinal shift to side of collapse. For other causes of unilateral homogenous shadow (increased density of a hemithorax)

been unsuccessful. The presence of an air bronchogram in the area of persistent atelectasis indicates that bronchoscopy is unlikely to help.

b. ***Peripheral obstructive collapse*** – is collapse with a patent bronchus. The site of obstruction is in more distal bronchi, beyond the fourth or fifth generation.

CAUSES – This type of collapse is commonly seen in resolving pneumonia, postoperative patients particularly following thoracic or upper abdominal surgery, critical care patients and asthmatic or eosinophilic lung conditions.

CLINICAL FEATURES – Signs of hemithoracic volume loss with percussion dullness, tubular bronchial breath sounds, positive whispering pectoriloquy, aegophony and bronchophony and crackles. The breath sounds and voice sounds are well conducted from the patent bronchus to the chest wall by the airless collapsed lung.

CHEST RADIOGRAPH – Signs of collapse with open bronchus sign on a penetrated film.

Right middle lobe (RML) syndrome (Brock's syndrome) – Isolated collapse of the right middle lobe is commonly due to non-specific lymphadenitis or malignant tumour. Radiologically the collapsed middle lobe causes obliteration of the right cardiac silhouette and is seen as a triangular paracardiac shadow on the lordotic film. CT scan and bronchoscopy can be used to identify the cause.

Contraction collapse (Fibrotic or cicatricial collapse) – It results from scarring of the lung, e.g. tuberculosis, silicosis, ankylosing spondylitis, sarcoidosis, hypersensitivity pneumonitis.

Adhesive collapse – Abnormality of surfactant system is the mechanism for collapse in conditions like ARDS and radiation injury.

2. **Compression atelectasis** (Relaxation collapse):

CAUSES – Pleural effusion, pneumothorax, large neoplasm or rarely cyst in substance of lung with valve-like communication with bronchus.

CLINICAL FEATURES – Since the central bronchus is often patent, the clinical signs are similar to those of peripheral obstructive collapse.

DIAGNOSIS – The collapsed lung is evident radiologically, however in case of effusion, the fluid and the lung are both opaque, hence the lung shadow is not evident. On CT scan the density of the collapsed lung is different from the effusion particularly after contrast injection. Another useful sign on CT scan is presence of air bronchogram in the collapsed lung upto several bronchial generations.

3. **Atelectasis due to surfactant deficiency or dysfunction** - (a) Small airway patency not maintained resulting in increased alveolar surface tension. (b) Can result from ARDS in preterm neonates and meconium aspiration and pneumonia.

Helical or round atelectasis (RA): is a localised form of collapse associated with pleural disease. Also called folded lung syndrome, shrinking pleuritis with atelectasis, it presents radiographically as a round, oval or angular mass. A diagnostic CT and radiographic sign is 'Comet tail' sign or 'vacuum cleaner effect' which is due to the bronchovascular bundle crowded together due to the collapsed lung and extending into the hilum.

Causes: RA is associated with asbestos exposure, parapneumonic effusions, CHF, Dressler's syndrome, pulmonary infarct and tuberculous effusions. No treatment is required.

Plate or disk atelectasis (Fleischner's syndrome): These are 2–5 cm long transverse lines several millimeters thick at the lung bases, associated with reduced diaphragmatic motion, and due to collapse of small pulmonary subdivisions. Distinction from infarction is difficult and the two may coexist.

21. SLEEP APNOEA SYNDROME

Obstructive sleep apnoea (OSA) is part of a spectrum of sleep-disordered breathing ranging from simple snoring to profound hypoventilation and respiratory failure at night. It is characterised by repeated episodes of partial or complete upper airway obstruction during sleep, commonly associated with hypoxia, and usually terminated by arousal from sleep, resulting in daytime symptoms such as sleepiness (OSA syndrome). Table 63 gives definitions in sleep-disordered breathing.

RISK FACTORS FOR OSA

Obesity – (a) Fat deposition around upper airway can cause airway narrowing and increased airway resistance. (b) Abdominal obesity can reduce lung volume, further reducing upper airway size.

Craniofacial /genetic factors – With narrowing of upper airways, e.g. micrognathia, retrognathia, high arch palate, macroglossia, Down's syndrome, Marfan's syndrome, adenotonsilar hypertrophy.

Gender – Higher incidence in men may be related to effects of androgens on upper airway neuromuscular properties or central fat deposition, alternatively progesterone may protect against OSA. (OSA syndrome is more prevalent in postmenopausal women).

Table 63: Definitions in sleep-disordered breathing

Apnoea	Complete cessation of airflow for at least 10 seconds
Hypopnoea	50% reduction in airflow for at least 10 seconds
Obstructive event	Continued respiratory effort despite reduced airflow
Central event	Absent respiratory effort with absent respiratory airflow
Hypoventilation	An abnormal rise in $PaCO_2$ occurs during sleep, usually associated with oxygen desaturation, without specific respiratory events
Periodic respiration	Ventilation waxes and wanes (central apnoea to hyperventilation)
Apnoea-hyopopnoea index (respiratory disturbance index)	Number of apnoeic and hypopnoeic episodes per hour of sleep >5 is usually considered abnormal (except in elderly)
Periodic breathing (Cheyne-Stokes respiration)	Ventilation waxes and wanes (central apnoea to hyperventilation) during sleep
Oxygen desaturation index	Number of episodes of discrete oxygen desaturation (usually >3%) per hour of sleep.

Reduced muscle tone – Alcohol reduces upper airway muscle tone, increasing the number of obstructive events at night. Similar effects occur with sedatives and some neurological conditions.

Nasal obstruction – can lead to increased negative upper airways pressure during inspiration predisposing to OSA.

CLINICAL FEATURES OF OSA

See Table 64 for the clinical features of OSA.

Table 64: Clinical features of OSA

- Snoring
- Disturbed sleep
- Excessive daytime sleepiness
- Morning headaches
- Nocturia, enuresis
- Dry mouth/throat
- Reduced concentration
- Mood changes
- Reduced libido, impotence
- Nocturnal choking and gasping
- Nocturnal reflux
- Restless sleep, frequent awakening
- Mood changes (irritability, depression).

DIAGNOSIS

Polysomnography. This involves oximetry, direct recording of thoracic and abdominal muscles to assess breathing (apnoea and hypopnoea per hour), electro-oculography (EO) - eye movement and EEG to record patterns of sleep as usual. The apnoea-hypopnoea index is calculated by the average number of apnoea and hypopnoea per hour of sleep. Diagnosis of sleep apnoea is confirmed if AH1 ≥ 5 with mild OSA 5–15, moderate 16–30, severe >30 AH1.

CONSEQUENCES OF OSA

- **Impaired daytime functioning** (memory, sustained attention, vigilance)
- **Systemic hypertension**
- **Cardiovascular disease—**OSA is associated with attenuation of the usual fall in BP at night ('non-dipping') which may be an independent risk factor for cardiovascular disease
- **Overlap syndrome –** A combination of COPD and OSA can lead to earlier development of hypercapnia, pulmonary hypertension and cor pulmonale.
- Obesity-hypoventilation syndrome – Day time respiratory failure with hypercapnia and hypoxia in absence of significant lung disease in some obese patients.

MANAGEMENT

General – (a) Weight loss of 10–30% significantly reduces severity of OSA. (b) Avoidance of alcohol and sedatives. (c) Relief of nasal obstruction with medical therapy.

Specific –

Nasal CRAP therapy – Positive pressure is applied to upper airway via a nasal mask, providing a 'pneumatic splint' to maintain upper airway patency, over the entire length of the collapsible airway. CRAP improves daytime sleepiness, neurocognitive performance, mood and quality of life.

Mandibular advancement devices – If CRAP is not tolerated or accepted, a removable oral appliance during the night is an option. This device is snapped into the dental arches and keeps the jaw in an advanced position thereby preventing collapse of upper airways.

Drugs – Tricyclic antidepressants reduce REM sleep time and can improve OSA in patients with REM - predominant disease.

Surgery – (a) Adenotonsillectomy can be curative in children and adolescents. (b) Uvulopalatopharyngoplasty – Successful result is seen in about 50%. (c) Complex maxillofacial surgery can be effective in majority of patients.

Central sleep apnoea – is less common. Patients snore less, are seldom obese, and complain of night time awakening. The central drive to breathing is abnormal. The syndrome occurs as a consequence of primary alveolar hypoventilation following bulbar polio or brainstem surgery.

22. RESPIRATORY FAILURE

Respiratory failure can be defined in two ways:

- Failure of oxygenation resulting in PaO_2 <8.0 kPa
- Failure of ventilation resulting in $PaCO_2$ >6.7 kPa with accompanying acid-base changes

CAUSES OF RESPIRATORY FAILURE

Respiratory failure can occur due to varied etiology as given in Table 65.

CLINICAL FEATURES

Any combination of the features listed in Table 66 may be present.

Specific physical signs – depending on the cause (e.g. neurological signs if neuromuscular disease is suspected, chest wall deformities).

Interpretation of arterial blood gases

Hypoxemia – Normal PaO_2 declines with age from 13.3 kPa in childhood to about 9.3 kPa in the elderly due to deterioration in gas exchange efficiency as the lung ages. This results in increasing alveolar-arterial oxygen gradient (P_AO_2 - PaO_2). Calculation of P_AO_2 - PaO_2 allows hypoxemia caused by alveolar hypoventilation or altitude from other mechanisms (e.g. diffusion impairment, ventilation/perfusion mismatch, shunt). When hypoxemia is caused purely by alveolar hypoventilation P_AO_2 is decreased, and P_ACO_2 increased, and P_AO_2 - PaO_2 should be normal.

Acid-base balance – pH indicates whether there is tendency towards acidosis or alkalosis. In the acute setting of respiratory disturbance, every 0.13 kPa rise in $PaCO_2$ is associated with a 0.01 fall in pH.

MANAGEMENT

1. ***Control of primary disease***– e.g. antibiotics for chronic bronchitis or fulminating pneumonia.
2. ***Maintenance of patent airway***– Nasal catheter to remove secretions and stimulate expulsive coughing. If secretions cannot be cleared by simple means, tracheostomy or endotracheal tube.

Table 65: Causes of respiratory failure

Airway obstruction (Limits airflow and thus reduces airway ventilation)
Upper airway
• Obstructive sleep apnoea
• Trauma
• Angio-oedema
• Stevens - Johnson syndrome
• Inhaled foreign body
• Acute epiglottitis
Lower airway
• COPD
• Asthma
• Bronchiectasis
• Cystic fibrosis
• Bronchiolitis obliterans
• **Disorders of lung parenchyma**
Acute
• Acute respiratory distress syndrome
• Pneumonia
• Acute pulmonary oedema
• Acute pulmonary embolism
• Acute fibrosing alveolitis
• Severe ARDS
Chronic
• Chronic fibrosing alveolitis
• Pneumoconiosis
• Sarcoidosis
• **Disorders of respiratory muscle pump**
Neurological
• Brainstem disease
• Amyotrophic lateral sclerosis
• Over-sedation
• Post-poliomyelitis syndrome
• Guillain-Barré syndrome
• Central sleep apnoea
• Cervical cord trauma
Musculoskeletal
• Kyphoscoliosis
• Myasthenia gravis
• Muscular dystrophy
• Congenital myopathy
• Chest wall trauma

Table 66: Clinical features of respiratory failure

1. **Due to hypoxemia**
• Restlessness
• Poor peripheral circulation
• Mental confusion
• Depressed level of consciousness
• Sweating
• Tachycardia
• Central cyanosis
• Cardiac arrhythmias
2. **Due to hypercapnia**
• Breathlessness
• Headache
• Warm extremities
• Bounding pulse
• Elevated BP
• Papilloedema occasionally
• Cardiac dysrhythmias (commonly multifocal atrial tachycardia)
• Muscle twitching
• Effects on CNS functions:
– Asterixis
– Hyporeflexia
– Miosis
– Confusion and coma
– (CO_2 narcosis).

3. ***Oxygen therapy***– The aim of oxygen therapy is to control hypoxemia without allowing CO_2 retention to threaten life from respiratory acidosis. This can be achieved by: (a) Low concentration of O_2 1–2L/min. by nasal cannulae or calibrated Venturi mask and titrating PaO_2 to 8.0–9.3 kPa. (b) High flow systems increase effect of inspired oxygen concentration (FiO_2). (c) Continuous positive airway pressure can be added via a tight fitting face-mask to recruit collapsed alveoli and improve gas exchange. When oxygen systems fail to sustain adequate PaO_2 further intervention (intubation, mechanical ventilation) is needed.

Long-term supplemental oxygen therapy (LTOT) is required in chronic severe hypoxemia.

4. ***Treatment of acidosis***– with IV sodabicarb. Acidosis corrects itself if adequate alveolar ventilation is maintained.
5. ***Treatment of failure of ventilation by mechanical ventilatory assistance*** –

NON-INVASIVE VENTILATION (NIV) is the provision of ventilatory support without instrumentation of the airway. It can be achieved with positive pressure administered through a well-fitting mask.

Table 67: Indications for ventilation

• Increasing respiratory rate
• Asynchronous respiratory pattern
• Altered mentation and conscious level
• Frequent oxygen desaturation despite increasing O_2 concentration
• Hypercapnia and respiratory acidosis
• Circulatory problems, including hypotension and atrial dysrhythmias

Criteria for NIV in Hypoxemic Respiratory Failure

- Dyspnoea
- Respiratory rate > 30 breaths per minute
- $PaO_2 : FiO_2 < 200$

Contraindications: NIV may not be appropriate in end-stage disease or in patients with several comorbidities. It is not used in patients having altered sensorium.

Monitoring: Continuous monitoring of oxygen saturation by pulse oximetry and regular assessment of arterial blood gas tensions and respiratory rate. Comparison of pH and respiratory rate immediately before NIV is started and at 4 hours is a useful measure of the success of NIV. When both improve success is very likely.

INVASIVE MECHANICAL VENTILATION – Mechanical ventilators provide a substitute for the respiratory muscle pump (Table 67).

Types of ventilators and principles of ventilation – Ventilators may be divided into – (a) Volume pre-set machines, in which rate and tidal volume are used to determine the minute volume delivered. Airway pressure is then a consequence of the set volume and total compliance of the system. The main advantage of this type of machine is guaranteed minute volumes despite changing lung mechanics (e.g. sudden onset of pulmonary oedema). (b) Pressure pre-set machines in which the volume of gas delivered in each machine-driven breath (tidal volume) is determined by the driving pressure of the gas and the compliance of the system in which gas is injected. This includes the chest, the chest wall and the machine / tubing interface. Pre-setting of the airway drive pressure prevents excessive airway pressures, but at the cost of unpredicairway delivery.

Common terminologies used in mechanical ventilation are given in Table 68.

Tracheostomy and Weaning

Tracheostomy is usually performed between day 7 and day 14 in patients in whom prolonged ventilation is likely.

Table 68: Terminology in mechanical ventilation

Type	*Explanation*
Continuous positive airway pressure (CPAP)	Not a form of ventilation, because there is no inspiratory/expiratory cycle. Can be used only in spontaneously breathing patients
Positive end-expiratory pressure (PEEP)	Involves addition of an above-atmospheric pressure to the expiratory cycle of a ventilated breath. Fulfils same function as CPAP in spontaneously breathing patients
Controlled breath	A pre-set, machine-delivered breath that cannot be altered by the patient
Assisted breath	A machine-driven breath that is triggered by patient effort. Volume and duration of breath may also be under patient control
Synchronized, intermittent mandatory ventilation (SIMV)	A volume pre-set mode allowing spontaneous breathing between machine-triggered breaths. Aims to prevent simultaneous machine-initiated and patient-initiated breaths ('fighting the ventilator')
Pressure controlled ventilation (PCV)	A pressure pre-set mode of controlled ventilation; both inspiratory and expiratory pressures are pre-set
Pressure-support ventilation (PSV)	A patient-triggered form of ventilation. Following a patient-initiated breath, tidal volume is augmented by the machine-driven present pressure. Often used in conjunction with PCV to allow spontaneous breaths, and as a weaning mode.

Weaning – Daily trials of spontaneous breathing through a 'T-piece' circuit and gradual reduction of ventilatory assist using pressure-support ventilation has been shown superior to SIMV in weaning. Only awake, cooperative patients can be weaned, and daily cessation of sedation improves weaning and outcome in the critically ill.

23. ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Adult respiratory distress syndrome (ARDS) is a common response to various pulmonary insults (Table 69); the genetic term is acute lung injury (ALI), and the term ARDS is reserved for its more serious manifestations.

PATHOGENESIS

Lung injury may be a primary event (e.g. inhalation), secondary to systemic inflammatory stimuli, or a combination of both (e.g. infection). ALI tends to be one of the earliest manifestations of generalized inflammatory states, and ALI caused by primary lung injury may lead to a systemic inflammatory state, culminating in multiorgan dysfunction.

Mechanisms Involved

ARDS is characterized by diffuse alveolar epithelial and endothelial damage. It can be divided into three stages:

1. *Exudative phase* – In first few days, alveolar interstitium is infiltrated by inflammatory cells, and alveolar spaces filled with proteinosis and haemorrhagic fluid.
2. *Proliferative phase* – The alveolar exudate resolves or undergoes organization over the next week or so.
3. *Fibrotic phase* – Fibrosis occurs after 3–4 weeks. Cyst formation and honeycomb changes occur particularly in dependant lung. Gradual reversal of fibrotic changes is usual in survivors.

CLINICAL FEATURES

Latent period – between time of initial insult and onset of respiratory symptoms 4–24 hours.

Symptoms

Dyspnoea – acute in onset or developing over several hours. Dry cough.

Cyanosis – may not be apparent, despite marked hypoxemia.

Tachypnoea – leads to hypocapnia, causing superficial vasoconstriction and a pale, waxy complexion. However patients with established ARDS due to sepsis may have hyperdynamic circulation due to increased basal metabolism with warm peripheries.

Signs

Initially normal but within 24 hours non-specific signs appear including widespread crackles and wheezes and diminished basal breath sounds.

With progression – (a) Sepsis. (b) Failure of other organs – Abnormal haematological indices (reduced

Table 69: Causes of ARDS

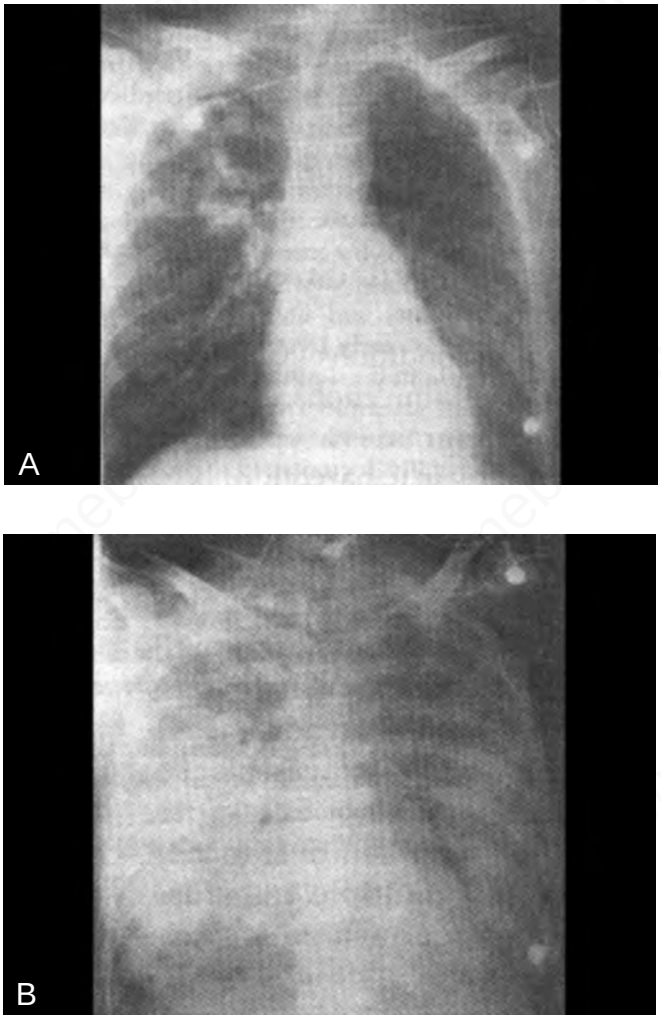
1. ***Respiratory*** (Direct injury):
   - Aspiration injury
     - Gastric juice
     - Chemicals
     - Smoke
     - Drowning
   - Embolization
     - Amniotic fluid
     - Fat embolism
   - Neurogenic pulmonary oedema.
   - Drugs (e.g. heroin, aspirin, paraquat, heparin, protamine).
   - Pulmonary contusion.
   - Oxygen toxicity.
   - Pneumonia (bacterial, viral, fungal or drug-induced e.g. bleomycin).
   - Disseminate TB.
   - Pulmonary vasculitis.
   - Thoracic radiation.
2. ***Non-respiratory*** (Indirect injury):
   - Severe sepsis
   - Tropical conditions – Cerebral malaria, tetanus, salmonella infections, amoebiasis, acute gastroenteritis (gram -ve septicaemia), rabies.
   - Poisoning (e.g. narcotic or organophosphorus compounds).
   - Acute pancreatitis.
   - Severe burns.
   - Major extra-thoracic trauma.
   - Post-cardiopulmonary bypass.
   - Steven-Johnson syndrome.
   - Disseminated intravascular coagulopathy.
   - Miscellaneous – Eclampsia, hepatorenal failure, liver cell dysfunction, high altitude, seizures, multiple transfusions or massive hemorrhage, metastatic carcinoma.

platelet count, increased fibrinogen degradation products), shock, kidney failure, liver failure, ileus, CNS depression and metabolic derangements.

COURSE – ARDS tends to reach its maximal initial severity over the next 24–48 hours, and may be rapidly fatal if severe and untreated. Acute deterioration of stable or improving ARDS can be due to chest infection, pneumothorax or systemic complications such as septicemia, hypotension or DIC.

INVESTIGATIONS

1. *Chest radiograph* – Initially normal but within 24–48 hours diffuse ill-defined patchy shadowing of nonspecific appearance is seen (Fig. 54A). The early changes of interstitial oedema rapidly become confluent (snowstorm or whiteout appearance) (Fig. 54B).
2. *Arterial blood gas analysis* – PaO_2 reduced and may be as low as 4–5 kPa despite FiO_2 of 0.4–0.6 (40–60%) or more.
3. *Tests for presence of other organ dysfunction* – Renal, hepatic, haematological parameters.
4. *Bacteriology* – Blood culture, culture of tracheal aspirate and culture of bronchoalveolar lavage in patients with nosocomial pneumonia.



Figs 54A and B: Adult respiratory distress syndrome. (a) Early changes show bilateral infiltrates (b) Bilateral white-out

COMPLICATIONS

1. **Early**– (a) Due to anaesthesia and muscle paralysis necessary for intubation. (b) Aspiration due to loss of protective laryngeal reflexes. (c) Reduction in cardiac

output due to decreased venous return as a result of initial positive pressure breaths. (d) Barotrauma and pneumothorax from positive intrapulmonary pressure.

2. **Later complications**– (a) Local trauma from endotracheal tube. (b) Damage to lungs and fibrosis – due to high O_2 concentration. (c) Barotrauma may occur when stiff lungs require high inflation pressures to achieve adequate ventilation or if emphysematous bullae are present. (d) Intrinsic positive end expiratory pressure (PEEP) – During lung deflation, relatively proximal.

MANAGEMENT

1. ***Removal of underlying cause*** – if possible, e.g. broad spectrum antibiotics for sepsis, drainage of infected fluid collections, removal of necrotic tissue.
2. ***Support of the injured lung*** **–** by restoration and maintenance of adequate tissue oxygen delivery. Most patients require ventilatory support. *Indications* – Severe respiratory failure, fatigue, tachypnoea, or evidence of circulatory inadequacy (e.g. lactic acidosis, poor tissue perfusion, hypotension).

   The purpose of respiratory support is to achieve adequate arterial oxygenation without exacerbating the underlying lung injury. The usual aims are low respiratory rate (< 10–14/minute), low tidal volume (6–8 mL/kg), relatively high positive end-expiratory pressure (5–20 cm H_2O).
3. ***Additional measures***
   a. **Prone positioning** – is most effective in early exudative phase of lung injury when it allows recruitment of alveoli, improving ventilation/perfusion matching. There are also cardiovascular benefits.
   b. **Inverse ratio ventilation –** In this method inspiratory time is increased so that it is longer than expiratory time. With decreased time to exhale, dynamic hyperinflation leads to increased end expiratory pressure which is similar to ventilator provided PEEP
   c. **High-frequency ventilation (HFV)** – entails ventilating at extremely high respiratory rates (5–20 cycles per second) and low VTs (1–2 mL/kg).
   d. Use of partial liquid ventilation (PLV) with perfluorocarbon (inert, high density liquid that easily solubilizes oxygen and carbon) has shown improvement in pulmonary function of ARDS patients with no survival benefit.
   e. Lung-replacement therapy with extracorporeal membrane oxygenation (ECMO), which provides a clear survival benefit in neonatal respiratory distress syndrome, may also have utility in selected adult patients with ARDS.
   f. **Nitric oxide and nebulized prostacyclin** – Low concentrations (1–20 ppm) nitric oxide acts as a local vasodilator in the vicinity of ventilated alveoli reducing shunt. The same effect is achieved with nebulized prostacyclin.
   g. **Corticosteroids** – may be beneficial in ARDS caused by inflammation (e.g. acute pancreatitis) rather than sepsis. They may also hasten recovery and improve outcome in those with severe pulmonary fibrosis or persistent ARDS.
   h. **Reduction of lung water** – Excessive extravascular lung water may result from over-enthusiastic fluid replacement, or from severe pulmonary leak, reflecting the severity of inflammatory insult. Hence management includes attempts to keep the patient dry; this is reasonable in well-resuscitated patients with adequate circulation, but is inappropriate in septic patients with evidence of poor tissue perfusion, in whom inadequate fluid replacement increases risk of multiorgan dysfunction.
4. **Prevention of complications**
   a. ***Multiorgan failure*** – Common reasons are failure to treat the initiating insult and failure to re-establish adequate circulation. Restoration of adequate circulation requires colloids or crystalloid and combination of inotropes, vasopressors or vasodilators.

Note **–** The oedema in ARDS is an exudate rather than a transudate, and mortality is related more to multiorgan dysfunction rather than to hypoxia.

   b. ***Nosocomial infections*** – include ventilator-associated pneumonia and those from indwelling lines and catheters. Cultures should be taken if infection is suspected, (new pyrexia, rising WBC or C-reactive protein, deteriorating gas exchange or new shadows on chest radiography).
   c. ***Pneumothorax*** – is likely when excessive pressure or tidal volume is used, and in the late proliferative and fibrotic phase.
   d. ***Supportive measures*** – Patients who do not tolerate full enteral feeding may be partially enterally fed, with small hourly volumes of food supplemented by parenteral nutrition. Prophylaxis against 'stress' ulcer with H_2-antagonists and sucralfate.

24. SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

SARS is an acute respiratory illness of infective aetiology associated with a coronavirus so-called because of complex projections on its surface known as peplomers giving it the appearance of a halo (corona = halo).

MODE OF TRANSMISSION

The virus is spread by close person-to-person contact and possibly by direct contact with infected body fluids. High concentrations of viral RNA have been demonstrated in sputum. Viral RNA has also been demonstrated in plasma in low concentrations during the course of illness and in faeces and urine during convalescence.

CLINICAL FEATURES

Incubation period is usually 2–7 days. SYMPTOMS – (a) The illness begins with fever (38°C) sometimes with chills and rigor. Other symptoms include headache, malaise and myalgias. (b) Lower respiratory phase starts after 3–7 days with onset of dry cough or dyspnoea that may be accompanied by or progress to hypoxemia. In 10–20% of cases the respiratory illness progresses to ARDS.

INVESTIGATIONS FOR A SUSPECT CASE OF SARS

1. *Chest radiograph* may be normal during the febrile period and throughout the course of illness. However in substantial number, the respiratory phase is characterized by early local infiltrates progressing to more generalized, patchy, interstitial infiltrates. In later stages there may be bilateral areas of opacification.
2. *Haematology* – WBC counts are generally normal or decreased. At the peak of respiratory illness about half the patients have leucopenia with relative lymphopenia and thrombocytopenia.
3. *Serological tests* – Demonstration of antibodies: (a) ELISA detects a mixture of IgG and IgM antibodies and is positive about 21 days after infection. (b) Immunofluorescence assay detects IgM antibodies after 10 days of illness.
4. *Molecular biological tests* – Polymerase Chain Reaction (PCR) can detect genetic material of SARS virus in clinical specimens such as blood, stool, respiratory secretions, urine or body tissue.
5. *Demonstration/Culture of SARS virus* – The coronavirus can be demonstrated in respiratory secretions, stool or urine by negative stain electron microscopy.

PROGNOSIS

The disease is usually associated with a worse prognosis if co-infection with other pathogens such as Chlamydia, paramyxovirus or hepatitis B is present.

MANAGEMENT

Antibacterial Treatment

- Levofloxacin 500 mg once daily intravenously or orally
- Or Clarithromycin 500 mg twice daily orally plus Co-amoxiclav 375 mg three times daily orally if patient <18 years or pregnant.

Ribavirin and Methylprednisolone

Add combination treatment with ribavirin and methylprednisolone with:

- Extensive or bilateral chest radiographic involvement
- Or persistent chest radiographic involvement and persistent high fever for 2 days
- Or oxygen saturation < 95% in room air.

Standard Corticosteroid Regimen for 21 days

Methylprednisolone 1 mg/kg every 8 h (3 mg/kg daily) intravenously for 5 days

Then methylprednisolone (1 mg/kg daily) intravenously for 5 days

Then prednisolone 0.5 mg/kg twice daily (1 mg/kg daily) orally for 5 days

Then prednisolone 0.25 mg/kg daily orally for 3 days

Then off.

Ribavirin Regimen for 10–14 days

Ribavirin 400 mg every 8 h (1200 mg daily) intravenously for at least 3 days (or until condition becomes stable)
Then ribavirin 1200 mg twice daily (2400 mg daily orally).

Pulsed Methylprednisolone

Give pulsed methylprednisolone if clinical condition, chest radiograph, or saturation worsens (at least two of these), and lymphopenia persists.
Give methylprednisolone 500 mg twice daily intravenously for 2 days, then back to standard corticosteroid regimen.
Ventilation – Consider non-invasive ventilation or mechanical ventilation if oxygen saturation < 96% while on > 6 L per min. oxygen or if patient complains of increasing shortness of breath.

25. SYSTEMIC DISEASES AND THE LUNGS

AUTOIMMUNE DISORDERS AND VASCULITIS

Rheumatoid Arthritis

Interstitial pneumonia – Clinical and radiological features identical to cryptogenic fibrosing alveolitis.

Pleural involvement – Rarely pleuritis and pleural effusions with high rheumatoid factor titre.

Airway involvement – Obliterative bronchiolitis. Inspiratory RHCT reveals a 'mosaic pattern' that is more prominent on full expiration because of gas trapping in the affected secondary pulmonary nodules.

Rheumatoid nodules – solitary or multiple, often a chance finding on chest radiography.

Infection – Bacterial low respiratory tract infection occasionally complicated by empyema.

Systemic Lupus Erythematosus

Interstitial disease – Alveolitis (rare), may be associated with diffuse alveolar hemorrhage

Pleural involvement – Pleurisy presenting symptom in about 10% and in 40–60% at some stage.

Pulmonary hypertension – though uncommon may result from pulmonary vasculitis, thrombosis and pulmonary artery vasoconstriction.

'Shrinking lung' – Rare syndrome with progressive reduction in VC and loss of lung volume on chest radiography.

Antiphospholipid syndrome – SLE patients may be at increased risk of venous and pulmonary thromboembolism.

Systemic Sclerosis

Interstitial disease – Pulmonary fibrosis. HRCT and histological features often those of nonspecific interstitial pneumonia.

Pulmonary hypertension due to pulmonary artery involvement.

Aspiration pneumonia due to involvement of oesophagus with altered contractility.

Myositis

Both polymyositis and dermatomyositis are characterized by respiratory muscle involvement and interstitial pulmonary fibrosis.

Sjögren's Syndrome

Chronic bronchitis, mucus plugging, follicular bronchiolitis, lymphocytic interstitial pneumonitis, pleural effusions, pulmonary hypertension and lymphoma.

Ankylosing Spondylitis

Reduced respiratory excursion and restrictive ventilatory defect. Bilateral upper lobe fibrosis may develop and upper lobe cavitation, sometimes with aspergillosis.

Behcet's Syndrome

Pulmonary vascular involvement in about 5%. Presentation is usually with haemoptysis.

Relapsing Polychondritis

Progressive destruction of supportive cartilage in trachea and large airways can lead to large airway collapse during expiration. Patients present with breathlessness and wheeze that can mimic asthma.

RENAL DISEASE AND VASCULITIS (PULMONARY-RENAL SYNDROME)

Wegener's Granulomatosis

Upper respiratory tract, lung and renal involvement and antinuclear cytoplasm antibodies (ANCA) against neutrophil enzyme proteinase. Lung involvement may be a presenting symptom in the form of cough, haemoptysis, breathlessness or pleuritic chest pain. Upper respiratory tract involvement results in subglottic stenosis and presents with exertional breathlessness and stridor. Chest radiography may show pulmonary infiltrates or nodules which often cavitate.

Microscopic Polyangiitis

Patients may have haemoptysis and alveolar hemorrhage, the main risk factor for death.

Churg-Strauss Syndrome

Is characterized by history of asthma, blood eosinophilia and vasculitis affecting two or more organs. Chest radiography commonly shows bilateral, patchy, non-segmental consolidation.

Henoch-Schonlein Purpure

Is rarely associated with alveolar hemorrhage.

Anti GBM Antibody Disease

Lung hemorrhage is a presenting feature particularly in smokers.

GENETIC DISORDERS

Marfan's Syndrome

Emphysematous bullae leading to pneumothorax, and bilateral upper lobe pulmonary fibrosis.

Neurofibromatosis

Associated with progressive interstitial pulmonary fibrosis in 30% of adults; this may progress to respiratory failure. Large paraspinal neurofibroma may be associated with kyphoscoliosis and respiratory failure.

Tuberous Sclerosis

Female patients may develop pulmonary lymphangioleiomyomatosis with progressive destruction of the alveoli and oestrogen-dependent smooth muscle proliferation. Patients may present with progressive exertional dyspnoea or pneumothorax.

GI DISORDERS

Inflammatory Bowel Disease

Bronchiectasis and obliterative bronchiolitis rarely with UC and Crohn's disease, mostly in patients with pancolitis.

Cirrhosis

Refractory hypoxemia caused by multiple microscopic (and occasionally) macroscopic A-V shunts between small precapillary pulmonary arteries and veins. In severe portal hypertension anastomoses may develop between pulmonary and hepatic circulation.

Pancreatic Disorders

Acute pancreatitis is associated with acute pneumonia and lung injury that may develop into ARDS. Pleural effusion which is typically left-sided.

Disorders of Upper GI Tract

Gastro-oesophageal reflux is believed to be the underlying cause of chronic cough in one third of patients. Aspiration of large volumes may be seen in those with a pharyngeal pouch, oesophageal disease related to scleroderma, neuromuscular disease or alcoholism. All of these present with recurrent aspiration (usually lower lobe) pneumonia.

ENDOCRINOLOGICAL DISORDERS

Obesity

Is a common cause of reduced VC, small static lung volumes and reduced compliance. When excess fat lies in a truncal distribution, obesity is associated with OSA.

Acromegaly

Is associated with large lungs, trachea and bronchi. Macroglossia and enlargement of other soft tissues of upper airway can lead to OSA.

Thyroid Disease

Thyroid goitre can cause tracheal displacement and compression. Airway obstruction may be intrathoracic or extrathoracic, and may be associated with stridor, reduced PEF, characteristic abnormality of maximum inspiratory and expiratory flow-volume loop. Both hyperthyroidism and hypothyroidism may cause respiratory muscle dysfunction.

Diabetes Mellitus

Increased risk of lung infection including TB. Gross hyperventilation (Kussmaul's respiration) is a feature of diabetic ketoacidosis.

NEUROLOGICAL DISEASE

Guillain-Barré Syndrome

Progressive weakening of respiratory muscle pump can lead to type II respiratory failure.

Motor Neuron Disease

Oropharyngeal muscle involvement can cause dysfunctional swallowing and aspiration pneumonia. Progressive weakness of respiratory muscles leads to type II respiratory failure, a common mode of death.

HAEMATOLOGICAL DISORDERS

Pleural effusions in about 30% with lymphoma and may occur in leukaemia as a result of disease or opportunistic infection. About two-thirds of lymphoma patients have mediastinal or hilar lymphadenopathy, these compresses or invade larger airways, producing breathlessness and fixed wheeze. Great vein compression may produce SVC obstruction. The parenchyma may be involved at presentation in 10%, and in 30–40% parenchymal involvement occurs at some stage. Lymphoma may present as discrete masses that can coalesce or cavitate.

26. PLEURAL DISEASE

PNEUMOTHORAX

Pneumothorax is air in the pleural cavity. Air may enter the pleural cavity through the chest wall, mediastinum, or diaphragm, or from a puncture of the visceral pleura covering the lung. Primary spontaneous pneumothorax occurs in patients without clinical evidence of lung disease. Secondary spontaneous pneumothorax is related to parenchymal lung disease.

Causes

Spontaneous Pneumothorax

Primary spontaneous pneumothorax – Due to rupture of apical subpleural bleb (benign spontaneous pneumothorax). Most common in young men. Exclusively seen in smokers.

Secondary spontaneous pneumothorax –

- *Rupture of* – Subpleural TB focus (active lesion or local emphysematous area from old scarring). Emphysematous bullae. Congenital cysts and bullae. Honeycomb lung. Oesophageal rupture.
- *Infections* (other than TB) – Bacterial pneumonia, lung abscess, Pneumocystis jiroveci pneumonia, whooping cough, bronchiectasis.
- *Diffuse fibrosing pulmonary disease:* Sarcoidosis, Pneumoconiosis Interstitial fibrosis.
- *Asthma* – Chronic bronchitis and emphysema.
- *Cystic fibrosis.*
- *Neoplasms* – Bronchial or pleural.
- *Secondary* to *spontaneous mediastinal emphysema.*
- *Pulmonary infarction.*
- *Miscellaneous:* Rheumatoid lung disease, Histiocytosis X, tuberous sclerosis, Marfan's syndrome, Ehlers - Danlos syndrome, Endometriosis of pleura, pulmonary alveolar proteinosis, idiopathic pulmonary haemosiderosis.

Traumatic Pneumothorax

a. *Penetrating trauma* – e.g. stab wounds, gunshot wounds, primarily by injuring the peripheral lung.
b. *Blunt trauma* can lead to rib fracture and cause increased intrathoracic pressure and bronchial rupture manifested by 'fallen lung sign (ptotic lung sign)' hilum of lung is below expected level within chest cavity.

Pulmonary barotrauma – at high altitude of 3050 m or in scuba divers.

Chest aspiration, transbronchial biopsy, needle aspiration lung biopsy, intercostal nerve block, subclavian cannulation, positive pressure ventilation, transthoracic liver biopsy, surgical procedures at base of neck, chest compression injury (including external cardiac massage).

Iatrogenic pneumothorax – may be a complication of a transthoracic puncture or a puncture of the subclavian vein.

Mediastinal emphysema is due to passage of air from the lung to the mediastinum and may occur during coughing or an extreme Valsalva manoeuvre. It is suspected when subcutaneous emphysema occurs at the upper chest and the neck level.

Catamenial pneumothorax – Rare condition occurring in females of 25–30 years. Repeated attacks of spontaneous pneumothorax occur usually on right side in association with menstruation generally within 48 hrs before or after onset of menstruation.

Symptoms

Vary depending on – (a) amount of air in the pleural sac, (b) rapidity of its accumulation, (c) condition of the lungs.

1. *Insidious onset* – Vague discomfort in chest, later shortness of breath on exertion. In tuberculous spontaneous pneumothorax the onset is not always sudden as the condition commonly occurs in patients suffering from advanced pulmonary TB which has already cut down their normal activities. Patient may complain of more breathlessness or may have chest pain, or the pneumothorax may be latent and detected by routine chest examination.
2. *Sudden onset* – Feeling of something snapping in the chest, severe pain, shock, increasing shortness of breath. Blood streaked sputum, cyanosis, restlessness and collapse.
3. *If hydropneumothorax* – Splash of fluid in the chest when he jumps may be the first intimation to the patient.

Signs

'Hyper-resonance with silence'.

1. ***CLOSED PNEUMOTHORAX*** – The opening in the lung is very small and rapidly heals, thus allowing the lung to re-expand.

Inspection – (i) Diminished expansion on affected side. (ii) Bulging on the side of pneumothorax. (iii) Displacement of apex beat towards sound side.

Palpation – Trachea may be displaced.

Percussion – (i) Hyperresonance. (ii) If on the left side abolition of cardiac dullness. (iii) Right sided pneumothorax reduces upper level of liver dullness.

Auscultation – (i) VR absent. (ii) Breath sounds diminished or absent. Bronchial breath sounds described as metallic or amphoric may be heard. (iii) Crunching sound – In left-sided pneumothorax there may be 'crunch' over the heart if air is also present in mediastinum (Hamman's sign). (iv) Click – A shallow left pneumothorax may produce a sound synchronous with the heartbeat.

2. ***OPEN PNEUMOTHORAX*** – The opening remains patent and the pressure in the pleural space remains equal to that of the atmosphere. Signs same as above plus – (i) Cracked pot sound may be heard on percussion, (ii) on auscultation air can be heard passing to and fro through the opening, (iii) voice sounds and cough heard with metallic echo.

3. ***TENSION PNEUMOTHORAX*** – The opening is valvular and air can enter into the pleural space during inspiration but cannot escape during expiration so that a positive pressure occurs in the pleural cavity (Fig. 55). Tension

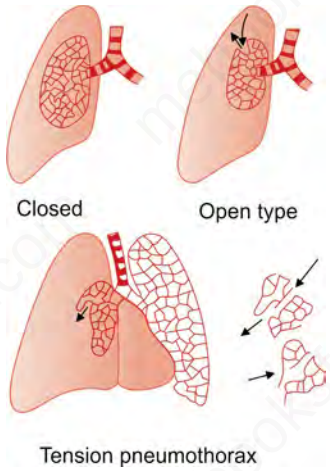


Fig. 55: Types of spontaneous pneumothorax. In closed pneumothorax the rupture gets sealed. In open type there is a bronchopleural fistula and the pleural pressure approximates atmospheric pressure. A check-valve mechanism leads to tension pneumothorax

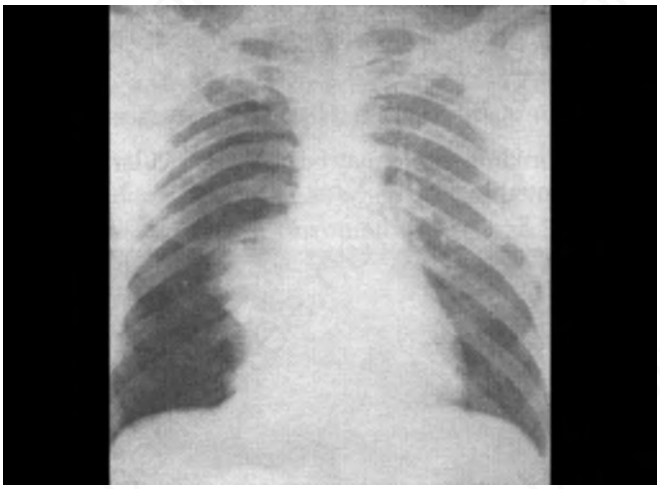


Fig. 56: Right sided spontaneous pneumothorax with partial collapse of right lung. For other causes of unilateral hypertransradiancy

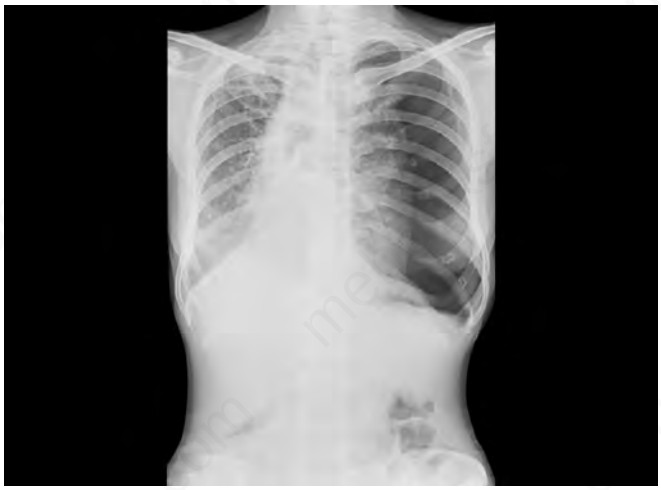


Fig. 57: X-ray chest shows left sided pneumothorax with underlying partial lung collapse of left lung, the trachea and mediastinum are pushed towards the right

pneumothorax may occur in clinical conditions such as ventilated patients, traumatic chest injuries, during cardiopulmonary resuscitation, patients undergoing hyperbaric O_2 treatment, blocked or displaced chest drains.

Signs are: (a) Displacement of mediastinum. (b) Increasing cyanosis and dyspnoea. (c) Increasing rapidity of pulse. (d) Distended neck veins. (e) Widening of intercostal spaces. (f) Hyperresonant or tympanic note; note dull if intra-pleural tension very high. (g) Downward displacement of liver if right sided pneumothorax, and of diaphragm. (h) Positive coin test.

Table 70: Chest radiograph findings

Visceral pleural white line	Convexity towards hilum
Absence of lung markings	Distal or peripheral to the visceral pleural white line
Displacement of mediastinum	Towards opposite side
Deep sulcus sign	On frontal view, larger lateral costodiaphragmatic recess than on opposite side Diaphragm may be inverted on side with deep sulcus
Total/subtotal lung collapse Radiographic signs in upright position	This is passive or compressive atelectasis Sharp delineation of visceral pleura by dense pleural space Mediastinal shift to opposite side Air-fluid level in pleural space on erect chest radiograph White margin of visceral pleura separated from parietal pleura Usually seen in the apex of the lung Absence of vascular marking beyond visceral pleural margin May be accentuated by an expiratory film in which lung volume is reduced while amount of air in pneumothorax remains constant so that relative size of pneumothorax appears to increase
Radiographic signs in supine position (difficult to see)	Anteromedial pneumothorax (earliest location) Outline of medial diaphragm under cardiac silhouette Deep sulcus sign

Imaging Studies

Chest Radiograph: Radiographic findings are enumerated in Table 70.

2. *Chest CT scanning:* A CT scan is more sensitive than a chest radiograph in evaluation of small pneumotho-

rax and pneumomediastinum. It is the gold standard for diagnosing occult traumatic pneumothorax not apparent on supine chest radiograph (Figs 56 and 57).

3. *Ultrasonography:* Ultrasonic features include absence of lung sliding. M mode imaging demonstrates an alternating pattern of absent lung sliding with normal lung sliding. This occurs at the boundary of pneumothorax where during inspiration the lung is seen to slide transiently and during expiration the sliding is abolished. This phenomenon known as the 'lung point' is 100% specific for pneumothorax and can be used to determine the size of the pneumothorax.

Recurrent spontaneous pneumothorax

- Presence of emphysematous bullae or subpleural apical bleb
- Cystic fibrosis
- Lung cysts
- Honeycomb lung
- Rupture of bronchogenic or oesophageal carcinoma
- With lymphangioleiomyomatosis

Bilateral pneumothorax: *Causes:*

- Cystic fibrosis
- Bilateral rupture of apical blebs
- Congenital cysts
- Bilateral primary spontaneous pneumothorax (rare)

Differential Diagnosis

1. ***Of common types of pneumothorax–***

Table 71 gives differences between benign and tuberculous pneumothorax.

2. ***Of causes of resonant note with diminished breath sounds–***

Table 72 gives differences between large pulmonary cavity and pneumothorax.

Table 71: Differences between benign and tuberculous pneumothorax

Benign pneumothorax	*Tuberculous pneumothorax*
No family history of tuberculosis	Family history of tuberculosis may be obtained
Fever usually absent	Pyrexia common
No loss of weight	Weight loss common
No sweats	Night sweats frequent
Other lung normal	Other lung may show signs of tubercle
Fluid accumulation minimal or absent	Fair amount of fluid may accumulate
No adhesions	Adhesions frequently present

3. ***Emphysematous bulla of large size*** – Symptoms of chronic bronchitis. Transient crackles on auscultation. X-ray – Fine lines in shape of crescents and semicircles. The circumscribed lung is hyperilluminated and adjacent tissue condensed. No intrathoracic displacements.
4. ***Pulmonary emphysema*** – Compensatory or localized type. Breath sounds accentuated. Signs of disease in lung, e.g., collapse or massive effusion.
5. ***Obstructive emphysema*** or emphysema due to ball valve type of obstruction of main bronchus – Mediastinum may be displaced to sound side. X-ray – Lung markings extend to periphery. On screening contrast in transparency of two lungs easily seen at end of expiration.

Table 72: Differences between large pulmonary cavity and pneumothorax

Pneumothorax	*Large pulmonary cavity*
Acute onset	Insidious onset
Chest pain	No chest pain
Absence of movements of chest on affected side	Restriction of movements at apex only
Bulging of interspaces	Retraction of interspaces
VR diminished or absent	Increased VR
Breath sounds absent	Cavernous or amphoric breath sounds
Cracked pot sound rare	Cracked pot sound usual if cavity superficial
Succussion splash may be present	No succussion splash
Bell tympany constant	Bell tympany rare

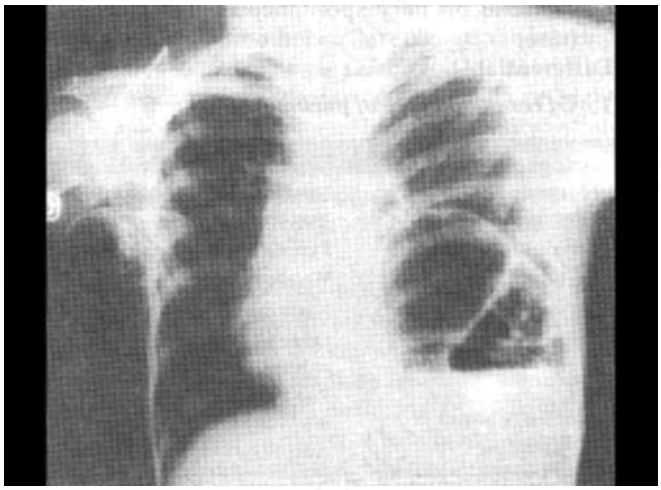


Fig. 58: Eventration of the left dome of diaphragm which is thin and markedly elevated. Bowel loops are seen just below the left diaphragm herniating into left hemithorax. A fluid level is present the left side and mediastinum is shifted to the right side

6. ***Congenital large cyst***– May be difficult to distinguish clinically from pneumothorax. X-ray – No evidence of collapsed lung at hilum. Delicate trabeculations may be seen.
7. ***Eventration of diaphragm*** (Fig. 58) – No symptoms or symptoms referable to gastrointestinal or circulatory system or lungs. Heightened inspiratory ascent of costal margin on affected side due to lack of opposition of paralysed diaphragm. X-ray –Diaphragm high in chest; paradoxical movement on fluoroscopy.
8. ***Hernia of stomach or colon through diaphragm***– Same signs as eventration. Differentiated by barium meal. In herniation, level of radio opaque mass visible on a higher plane than that of the oesophageal opening, in eventration the two levels coincide.
9. ***Subphrenic abscess***– History of abdominal illness or operation. Fever. Alternating zones of resonance and dullness from above downwards. Fluoroscopy – raised and immobile diaphragm.
10. ***Distension of stomach***– May cause left half of diaphragm elevated well above the nipple. Symptoms of dyspepsia. Normal chest expansion, bulging in left upper abdominal quadrant. Gurgling may be heard.

Hydropneumothorax (Fig. 59) – *Causes:*

1. Rupture of subpleural tuberculous focus (commonest cause)
2. Rupture of subpleural lung abscess (pyopneumothorax)
3. Pulmonary infarction
4. Penetrating chest injury (haemopneumothorax). Iatrogenic: After cardiac surgery, aspiration of pleural fluid, secondary infection of pneumothorax following water-seal drainage.

Diagnostic signs:

1. Shifting dullness – The upper limit of dullness is horizontal and shifts when patient's position is altered.
2. Succussion splash (Hippocratic succussion).
3. Tinkling sound may be heard particularly after coughing.

4. Horizontal level of fluid on percussion

CHRONIC PNEUMOTHORAX – Pneumothorax persisting for more than 3 months. *Causes* – 1. Failure of collapse of lung due to adhesion. 2. Air leak through congenital cyst. 3. Generalized emphysema causing multiple leaks.

Management of Pneumothorax

Medical

1. NO TREATMENT – Only observation if small pneumothorax (occupying less than 20% of the hemithorax) as the air usually gets absorbed within a few days. The exception is the patient with severe lung disease who cannot tolerate even a small pneumothorax and air has to be removed. Antituberculous therapy if evidence of tubercle.

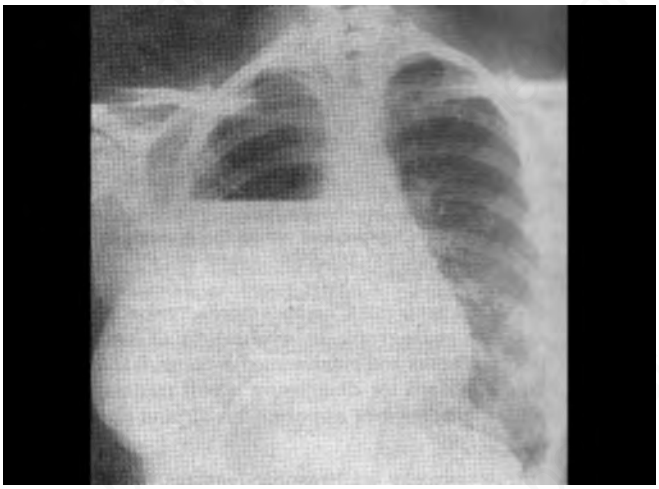


Fig. 59: Right-sided hydropneumothorax

2. SIMPLE ASPIRATION

Indications

- Significant dyspnoea
- Traumatic (minor)

Technique – Aspiration can be performed with a 16-guage IV cannula attached to a 50 mL syringe and a three-way tap. An intercostal space is selected from chest radiographs and after sterilizing the skin over the intercostal space, it is anaesthetised with lignocaine down to parietal pleura. The cannula is then inserted through the intercostal space and pneumothorax aspirated into the syringe, and expelled via the three-way tap. As a precaution, a plastic tubing is attached to the exit arm of the three-way tap and its end placed in a bottle of sterile water. This will ensure that with each turn of the tap, air is being drawn from the pneumothorax.

Aspiration is discontinued when gentle suction yields no more air from the pneumothorax, suggesting that the lung has fully re-expanded, or earlier if patient shows signs of distress. If more than 2 litres of air are aspirated, a chest radiograph should be repeated to judge the volume of re-expansion. Absence of re-expansion suggests a bronchopleural fistula and intercostal tube drainage should be resorted to.

Disadvantage

Chances of subcutaneous emphysema.

3. INTERCOSTAL TUBE DRAINAGE
   A. **Tube drainage –** Initial use of small tubes (10–14 F) in most cases:

Indications

- Aspiration fails to resolve
- Tension pneumothorax
- Air space more than 50% of pneumothorax
- Traumatic (major)
- Ventilated (barotrauma)

Procedure

a. *Site* – 2nd intercostal space in mid-clavicular line or sixth space in mid-axillary line. For women a basal drain is preferred to avoid an anterior chest scar. Chest radiographs should be used as a guide together with ultrasound if necessary.
b. *Position of patient* – For apical drain, patient must lie flat, for a basal drain slightly rotated towards the opposite side with the arm slightly raised.
c. *Local anaesthetic* – Upto 10 ml of 2% lignocaine to infiltrate skin, subcutaneous tissue, intercostal muscle and pleura.
d. *Needle aspiration* – as site of insertion to confirm presence of fluid.
e. *Skin incision* – just large enough for the cannula.
f. *Introduction of intercostal drain* into pleural space. After insertion, the intercostal tube should be clamped immediately to avoid air entering pleural space.
g. *Purse-string suture* around site of insertion and ends tied round the drain.
h. *Connecting the tube to underwater seal bottle.*
i. *Removal of clamp.*
j. *Taping tube to chest wall* at a distance from point of insertion to prevent it being pulled out.

Care of the drain – Level of fluid in the tube connected to the under-water seal bottle should rise and fall with breathing. If fluid level stops swinging, it suggests blocking of the intercostal tube, of its falling out of the pleural cavity, or obstruction of the tube by the fully inflated lung (can be confirmed by chest X-ray). Constant bubbling of air through the underwater seal indicates bronchopleural fistula.

Removal of tube – When bubbling of air ceases, a chest X-ray should be taken. If the lung has re-expanded, the tube should be clamped for 12 hours, X-ray repeated, and if lung is still fully expanded, tube is removed. Failure of expansion of the lung after 7 days or persistence of air leak, indicates further intervention.

B. **Indwelling catheter drainage** – Indications same as for large-bore tube drainage.
C. **Chemical pleurodesis** – via an intercostal drain. Advantage over thoracic surgical procedures is that it is safer in patients with terminal disease (malignant effusion) or compromised lung function.

Requirements – Pleural surfaces to be in apposition, and is hence unsuccessful if the lung is not fully re-inflated, or if air or fluid continue to drain. Large, symptomatic and recurrent malignant effusions should be drained prior to pleurodesis.

Procedure – (i) Insert an intercostal drain. (ii) Connect the underwater bottle seal to wall suction at 10–20 cm H_2O. (iii) Continue until no more fluid can be removed. Stop suction and clamp the tube close to the chest wall. (iv) Inject sclerosant, e.g. talcum powder 10 g in 50 mL saline. Use of sclerosant is painful and analgesic such as dimorphine should be given i.m. 30 minutes before instillation and qds subsequently. (v) Leave the drain for 1–4 hours before removing the clamp. (vii) Dress the wound and repeat chest radiograph.

Surgical treatment

Indications – 1. Bilateral pneumothorax. 2. Haemopneumothorax. 3. Persistent leak due to bronchopleural fistula. 4. Air leak that persists for more than 1 week. 5. Recurrent pneumothorax. 6. Patients whose occupation poses special risks, e.g. pilots, seamen.

Procedures:

1. *Surgical closure of bronchopleural fistula.*
2. *Thoracoscopy/thoracotomy and cauterization* – of the breach in the pleura, or excision of the bulla and oversewing of the defect.
3. *Pleurectomy* – Bullectomy and partial apical pleurectomy is surgical treatment of choice. Re-expansion of the lung then leads to obliteration of the pleural space.
4. *Decortication* – Stripping off of fibrin from affected visceral pleura.

Video-assisted thoracic surgery (VATS) is a technique that causes less operative pain, allows earlier discharge. However it is often unsuitable for a patient with chronic lung disease.

Other techniques

Indwelling small-bore catheter – is intermediate between simple aspiration and intercostal tube drainage methods. It allows the patient to remain mobile. A 24G catheter is connected to a flutter valve until the hole seals. This technique is useful in small air leaks, or to allow patients unsuitable for surgery to return home.

Table 73: Causes of pleurisy

1. *Infection* – Tuberculosis, pneumonia, bronchiectasis, lung abscess, infection with Coxsackie B virus (epidemic pleurodynia or Bornholm disease).
2. *Pulmonary infarction.*
3. *Bronchogenic carcinoma.*
4. *Injury to chest wall or disease of ribs.*
5. *Rheumatoid arthritis.*
6. *Systemic lupus erythematosus.*
7. *Uraemia.*
8. *Asbestos pleural disease.*
9. *Familial Mediterranean fever.*

Medical thoracoscopy – is intermediate between intercostal tube drainage and thoracic surgery. It is performed under sedation using a rigid instrument and allows – (a) Complete drainage of pleural fluid. (b) Pleurodesis with talc (more effective than chemical solutions). (c) Biopsy under direct vision of abnormal visceral and parietal pleura.

PLEURISY

See Table 73 for the causes of pleurisy. All pleural disorders with inflammatory exudation may start as fibrinous 'dry' pleurisy.

Symptoms

1. Pain in the side, sharp, stabbing or tearing, worse on coughing, deep respiration and pressure from outside. When the diaphragmatic pleura is affected the pain may be referred to the tip of the shoulder, or to upper abdomen from pleurisy affecting the lower lobes.
2. Rapid shallow breathing with unproductive cough.
3. Chilly sensations at onset and moderately intermittent fever.

Signs

1. Diminished movement on affected side.
2. Pleuritic rub – Crackling quality, heard during both inspiration and expiration, localised usually to a small area of chest wall, and often better heard on increasing the pressure of the stethoscope.

Management

1. Rest in bed.
2. Relief on pain with – (a) hot water bag, (b) splinting of chest with strapping, (c) analgesics and sedatives.
3. Relief of cough – Codeine preparations.
4. Specific treatment – according to cause of pleurisy.

PLEURAL EFFUSION

Pleural effusion is an accumulation of fluid in the pleural space as a result of excessive transudation or exudation from pleural surfaces. Pleural cavity normally contains less than 20 mL of fluid.

Mechanisms of Pleural Fluid Formation

- Increased pulmonary capillary pressure
- Decreased tissue oncotic pressure (e.g. hypoproteinemia)
- Decreased negative intrapleural pressure (e.g. atelectasis)
- Increased permeability of pleural membrane (e.g. pleurisy, malignancy)
- Obstruction of lymphatic flow (e.g. mediastinal nodal metastases)
- Transdiaphragmatic fluid flow from peritoneum (e.g. ascites from hepatic cirrhosis)

Causes

See Table 74 for the causes of pleural effusions.

Meigs' syndrome. Pleural fluid (hydrothorax) is associated with ascites due to an ovarian tumour (usually a benign fibroma), occasionally malignant disease. Resolution occurs if the tumors are removed. The same syndrome occurs with endometriosis. Small bilateral effusions are common with peritoneal dialysis, but occasionally the fluid collection is large, usually right sided and thus simulates Meigs' syndrome.

Symptoms

Onset – (i) Acute with attack of pleuritic pain or pyrexia of unknown origin, later with pain. (ii) Subacute. (iii) Insidious – with ill-defined health followed by dyspnoea.

1. Pain – in early stage due to dry pleurisy replaced by dull ache.
2. Dyspnoea – depends on rate of collection of fluid.
3. Cough usually dry.
4. Loss of weight.
5. Symptoms of toxaemia – Malaise, fever, anorexia.

Signs

About 500 mL of fluid is required to produce physical signs.

Inspection

1. With large effusion, orthopnoea or preference for lying on same side.
2. Diminished mobility of chest on one side.

Table 74: Causes of pleural effusions: Classification of pleural fluids.

Nature of fluid	*Causes*
1. **Serous**	
a. **Transudate** *(Hydrothorax)* Pale yellow Sp. gr. 1008–1012 Proteins < 3 gm. Does not clot Cells – few endothelial or none Fluid LDH < 200 IU	*Rare* • Constrictive pericarditis • Urinothorax • SVC obstruction • Ovarian hyperstimulation • Meigs' syndrome *Common* • LV failure • Liver cirrhosis • Hypoalbuminemia • Peritoneal dialysis *Less common* • Hypothyroidism • Nephrotic syndrome • Mitral stenosis • Pulmonary embolism
b. **Exudate** *(Effusion)* Yellow to brown Sp. gr. 1016 or more Proteins >3 gm. Clots spontaneously Pleural fluid protein : serum protein ratio >0.5 Pleural fluid LDH : serum LDH ratio >0.6 Pleural fluid LDH > two-thirds of upper limit of normal LDH	*Rare* • Drugs (Amiodarone, metoprolol, bromocriptine, NFT, phenytoin, methotrexate) • Fungal infections • Yellow nail syndrome *Common* • Tuberculosis • Postpneumococcal • Malignancy
2. **Purulent effusion** – *Empyema* *Character of pus:* Pneumococcus: Usually thick, greenish yellow with thick flakes of fibrin. Streptococcus: Thin, turbid and greenish in colour. May thicken later. Rheumatoid pleurisy : Turbid green fluid	*Less common* • Pulmonary infarction • Rheumatoid arthritis • Autoimmune diseases • Pancreatitis • Post-myocardial infarction syn. • Post-myocardial effusion • Benign asbestos effusion • Neoplastic implants on pleura. • Contusion of lung or chest wall. • Pulmonary infarction. • Tuberculosis. • Primary mesothelioma of pleura. • Rupture of pleural adhesions. • Anticoagulant therapy. • Haemophilia. • Acute aortic dissection. • Pleural endometriosis. • Pleuritis associated with amoebic liver abscess, benign pericarditis, or haemorrhagic pancreatitis. • Trauma to thorax • Haemorrhage from tumour implant. • Spontaneous haemopneumothorax. • Amoebic abscess of liver rupturing into pleural cavity. • Old cholesterol effusion. • Rupture of thoracic duct following trauma. • Malignant growth or mediastinal glands invading thoracic duct. • Tuberculosis. • Parasitic infection – Filaria. • Thrombosis of left subclavian vein • Carcinoma or tuberculosis of lung or pleura. • Mediastinal radiotherapy • Sarcoidosis • Amyloidosis
3. **Haemorrhagic fluid** *Blood-tinged exudate* *Frank blood* *Chocolate coloured fluid* (degenerating RBCs)	
4. **Opalescent fluid** – *(Chylous or milky)* *Chylothorax* – Pure chyle. High triglyceride level (> 110 mg/dL). Chylomicrons found. Many large fat globules. *Chyliform* – Fat but not derived from thoracic duct but from degenerated cells. Globules smaller. *Pseudochylothorax* (Cholesterol pleurisy) – Cholesterol level > 200 mg/dL, cholesterol crystals seen on microscopy	

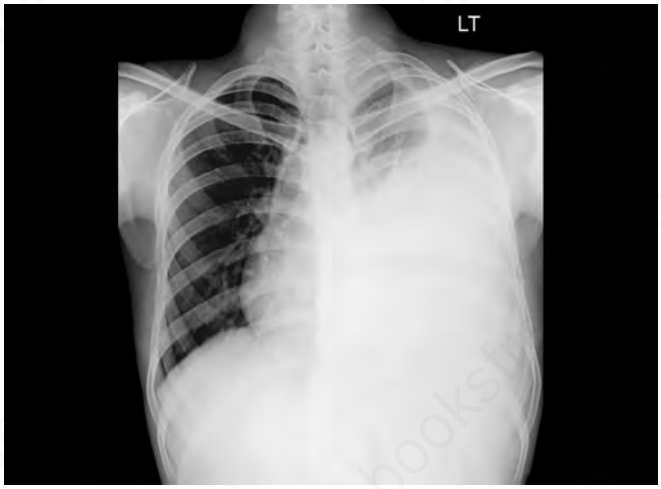


Fig. 60: Massive pleural effusion right with trachea and mediastinum pushed to the right

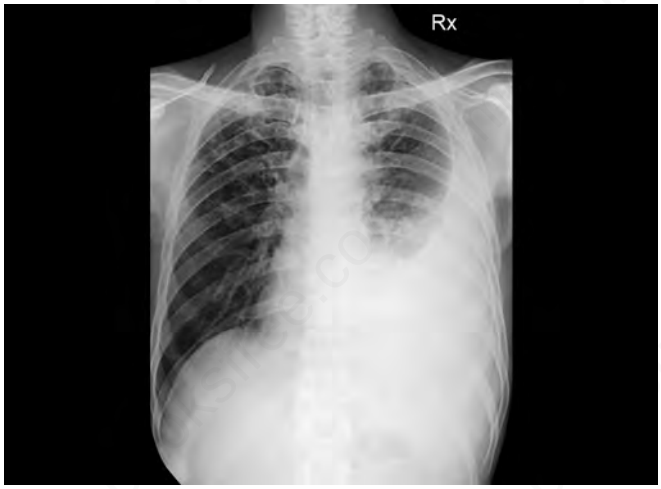


Fig. 61: Pleural effusion in left pleural sac

3. Bulging of intercostal spaces on affected side if large effusion in a thin person.
4. Fullness of hypochondrium if large effusion.
5. Apex beat may be displaced to opposite side unless small, malignant (associated with compression collapse) or loculated effusion.
6. Sternomastoid sign (Trail's sign) – Sternomastoid muscle on side of mediastinal displacement may be prominent.

Shift of trachea to same side in effusion – associated with bronchial Ca:

If absorption collapse – Shift to same side due to negative intrapleural pressure.

If compression collapse – Shift to opposite side due to positive intrapleural pressure.

Causes of absence of mediastinal shift in pleural effusion:

1. Small effusion.
2. Encysted effusion.
3. Bilateral effusion.
4. Apical fibrosis on same side.
5. Associated lobar collapse.

Palpation

1. Immobility of chest.
2. Displacement of trachea to opposite side.
3. Diminished or absent TVF.

Percussion

1. Dull note (absolute dullness).
2. Increased resistance to percussion.
3. Dullness rising from the spine, highest in posterior axilla and falling again towards the sternum – Ellis's S shaped curve.
4. Skodaic resonance or boxy note just above the effusion.
5. Triangular area of dullness against the vertebral column at base of opposite lung (Grocco's triangle).
6. Obliteration of Traube's semilunar space if fluid on left side.

Auscultation

1. Diminished or absent breath sounds.
2. Bronchial breathing in early stages because lung is compressed but bronchi are patent.
3. Diminished or absent vocal resonance.
4. Aegophony and whispering pectoriloquy just above the upper level of fluid.
5. No foreign sounds with large collection of fluid. Crackles if small or moderate amount.
6. Crackles may be heard at the base of the opposite lung due to congestion.
7. Heart sounds (and apex beat) may be obscured in case of large effusion on left side.

Investigations

1. **Imaging**
   a. ***Chest radiograph*** – Obliteration of costophrenic sinus on affected side with an opacity extending up the chest wall concave towards the lung on PA film in presence of about 200 ml Smaller effusions (50 ml) can be detected if radiograph is taken with patient in lateral decubitus position. Views taken in this position are also useful when a subpulmonary collection of fluid mimics an elevated dome of the diaphragm (Figs 60 and 61).

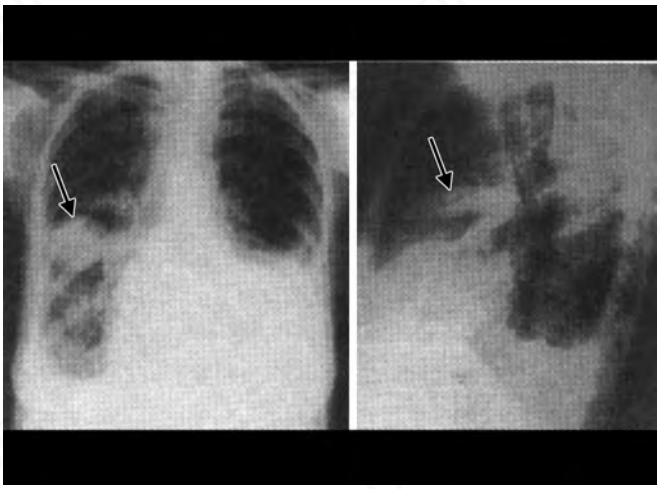


Fig. 62: Encapsulated fluid in the minor fissure

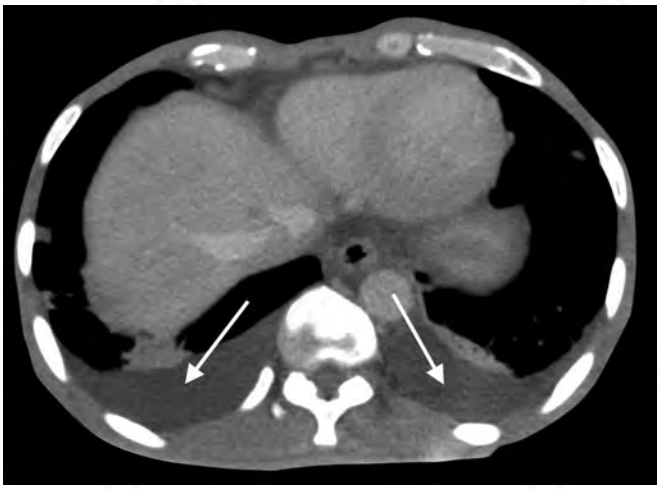


Fig. 63: CT chest showing bilateral pleural effusion

Table 75: Pleural fluid appearance and suspected disease

Observation	*Suspected disease*
• Putrid odour	Anaerobic empyema
• Food particles	Oesophageal rupture
• Yellow-green	Rheumatoid pleurisy
• Ammonia smell	Urinothorax
• Milky	Chylothorax/pseudochylothorax
• Bilious	Biliary fistula
• Black	Aspergillus infection
• 'Anchovy sauce' fluid	Ruptured amoebic abscess

Fluid which is encysted by adhesions or is within one of the pulmonary fissures is not free to move under the influence of gravity and may cause a pseudotumour image (Fig. 62).

Phantom tumour or vanishing tumour of lung– is collection of effusion in transverse fissure of the lung in CHF which clears with diuretic therapy.

Ultrasonography is more accurate than plain chest radiography for estimating pleural fluid volume, and also aids thoracentesis when effusion is small or localized. It is also useful in demonstrating fibrinous loculation, and differentiates fluid and pleural thickening.

CT can detect pleural abnormalities more readily. It should be performed with contrast enhancement, with which benign and malignant pleural thickening can usually be differentiated (Fig. 63).

2. **Examination of pleural fluid –**

Pleural fluid observations (Table 75)

pH: Low pleural fluid pH usually defined as <7.2, represents a substantial accumulation of hydrogen ions (normal pleural pH is about 7.6 because of accumulation of bicarbonate).

Disease causing pleural pH < 7.2 – Empyema, parapneumonic effusion, collagen vascular disease (particularly RA), oesophageal rupture, tuberculosis, advanced malignant neoplasm.

Cytology. Malignant effusions can be diagnosed from a single pleural fluid cytology specimen in about 60%. Adenocarcinoma is diagnosed more often than mesothelioma.

Differential cell counts have a minor role in assessment of a pleural effusion. Pleural lymphocytosis is seen in tuberculous effusions and malignancy, and eosinophilic pleural effusion are often not benign. Coronary artery bypass grafting often causes left sided pleural effusions containing small lymphocytes.

Microbiological studies – on any exudate of possible inflammatory origin and should include Gram stain, aerobic and anaerobic cultures, and mycobacterial cultures.

Immunology – (i) *Rheumatoid factor* in rheumatoid effusion. (ii) *Antinuclear factor* in connective tissue diseases. (iii) *Complement level* may be low in rheumatoid or SLE effusions, but also in malignancy and infection.

Additional Biochemical Tests – in some clinical conditions

- Glucose concentration – < 30 mg/100 mL is usual in rheumatoid effusions, but also found with malignant effusion.
- Amylase levels – High levels in effusion associated with pancreatitis. Occasionally in malignant effusions secondary to metastatic adenocarcinoma, and in pleural effusions caused by oesophageal perforation.
- Estimation of cholinesterase to differentiate pleural exudate from transudates. PF cholinesterase > 2000 IU and PF/S cholinesterase ratio of > 0.5 is taken as exudate and lower values as transudate.

Fig. 64: Abram's pleural biopsy punch

- Chylomicra or high triglyceride levels (more than 110 mg/dL) are diagnostic of chylous effusion. Lipoprotein electrophoresis should be performed in equivocal cases (triglyceride 50–110 mg/dL) to detect chylomicra.
- Adenosine deaminase (ADA) high in empyema and TB.
- Tuberculous effusion shows ADA level > 40 IU/L and Interferon-γ > 140 pg/mL.

3. **Percutaneous pleural biopsy** is of most value in diagnosis of granulomatous and malignant disease of the pleura. It should be performed in case of undiagnosed exudative effusions in whom cytology is non-diagnostic, and there is clinical suspicion of TB or malignancy.

   The Abram's pleural biopsy needle (Fig. 64) is most often used. At least four samples must be taken to optimize diagnostic accuracy, and these should be obtained from one site. Image-guided cutting needle pleural biopsy is more sensitive for diagnosis of pleural malignancy and should be the preferred biopsy method in patients with CT detectable pleural thickening.
4. **Thoracoscopy** is used when less invasive techniques have failed. The sensitivity for malignancy is more than 90%. During the procedure, all the pleural fluid can be removed and pleurodesis performed.

Differential Diagnosis

I. **Conditions above the Diaphragm:**

1. *Thickened pleura*

- History of long standing.
- Interspaces depressed.
- Dullness over base.
- No change on change of posture.
- Diminished breath sounds.
- Chest radiograph – Shadow not so dense or uniform.
- Upper level not well defined, no displacement of heart.

2. *Pleural effusion*

- History acute, of few weeks.
- Interspaces bulging.
- Flat note at base with Skodaic resonance above level of fluid.
- Area of flat note changed by posture.
- Breath sounds often absent.

Table 76: Differences between pleural effusion and pneumonia.

Pneumonia	*Pleural effusion*
Onset acute	Onset rarely acute
Rusty sputum	Dry cough
Impaired note	Flat note
No displacement of mediastinum	Mediastinum may be displaced
Outline of dullness irregular and limited	Upper level of dullness extends from sternum to spine
Bronchial breath sounds (absent if massive pneumonia)	Diminished or absent breath sounds
Crackles always present	Crackles rarely heard
Bronchophony over area of consolidation	Aegophony at upper level of fluid
Leucocytosis marked	Leucocytosis absent or moderate

Chest radiograph – Obliteration of costophrenic sinus.

Moderately large effusion causes a uniform dense opacity with curved upper level, the concavity facing upwards with the highest point in the axilla.

3. *Empyema* – Bulging of intercostal spaces, skin red and shiny with perhaps oedema of chest wall. Symptoms of sepsis. Leucocytosis.
4. *Hydrothorax* – Usually bilateral, if unilateral on right side. No pain in chest and no history of acute pleurisy. No fever. Evidence of cardiac, hepatic or kidney disease. Transudate.
5. *Lobar pneumonia*

Table 76 gives differences between pleural effusion and pneumonia.

6. *Fibrosis of lung* – Retraction of intercostal spaces, heart or trachea shifted to side of lesion. VR diminished. No stony dullness. Non-homogeneous opacity on X-ray.
7. *Massive collapse of lung* – Mediastinum drawn to same side. VR increased. Evidence of cause of collapse, e.g., mediastinal growth, etc. X-ray – Homogenous opacity.
8. *Bronchial carcinoma* – When extending to periphery gives similar signs or may be associated with pleural effusion. Haemoptysis, presence of pressure symptoms, progressive emaciation and cachexia. X-ray – shadow of growth or collapse of segment, lobe or lung.
9. *Large pericardial effusion* – Heart not displaced to right, area of dullness most marked in axillary region, normal pulmonary resonance at back. Heart sounds muffled or not heard.
10. *Mesothelioma of pleura* – Large mass of solid tissue obliterating pleural space. Associated with pleural effusion which is haemorrhagic, shows large endothelial cells and requires repeated tapping.

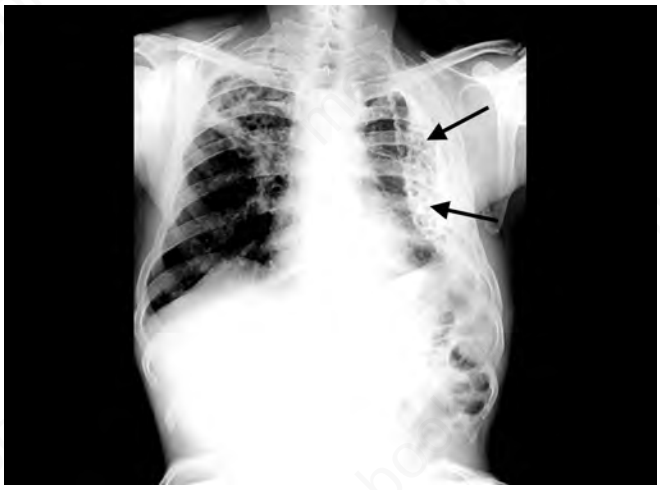


Fig. 65: Left-sided calcified pleural

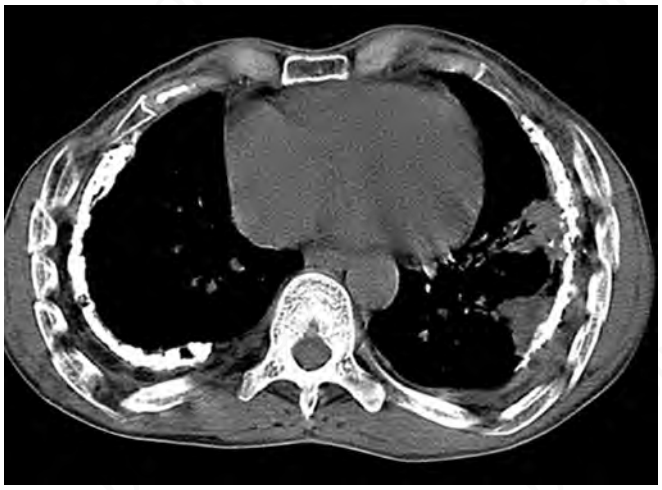


Fig. 66: CT chest shows bilateral crowding of ribs. Left lung shows two areas of consolidation abutting the chest wall. The anterior consolidation shows air bronchogram, there is bilateral armor or sheet like pleural calcification. There is crowding of ribs suspected and diagnosed based on history and imaging studies. Unilateral pleural calcification is likely to be the result of previous empyema, hemothorax or pleurisy

11. *Cardiac enlargement* – No dullness at base of lung, marked pulsation in epigastrium, apex beat in axilla. Evidence of cause, e.g. aortic regurgitation, etc.
12. *Hydatid cyst of lung* – If large, signs of effusion usually at base with sometimes displacement of mediastinum. Cough and progressive dyspnoea common. X-ray shows shadow with well-defined margins. Eosinophilia common.

II. **Conditions below the Diaphragm**

13. *Subphrenic abscess* – History of appendicitis, abdominal operation or biliary infection. Broad zone of hyperresonance just above the dull area. Fever with rigors, some pain in upper abdomen and rigidity in epigastrium.
14. *Liver abscess* – may push the diaphragm and lower border of pleura up and give signs of effusion. History suggestive of liver disease. No moveable dullness. Compression tenderness present.

Complications

- Acute pulmonary tuberculosis or miliary tuberculosis.
- Spread of disease to pericardium or peritoneum.
- Pulmonary oedema.
- Thrombosis of veins, e.g. superior or inferior vena cava or iliac or femoral veins.
- Sudden death probably due to pulmonary embolism.

Sequelae – (1) Pulmonary tuberculosis within 5–6 years. (2) Permanent collapse of lung. (3) Pleural thickening and calcification (Figs 65 and 66), adhesions and bronchiectasis.

Management

I. ***General*** – Rest in bed till fluid gets absorbed, nourishing diet, vitamins.

II. ***Chemotherapy***

a. *Tuberculous effusion* – Antituberculous therapy.
b. *Malignant effusion* – After complete aspiration, injection of Tetracycline hydrochloride 500 mg in 20 ml saline into pleural cavity via intercostal drain followed by further 20 ml saline. Tube is then clamped for 6 hours during which patient should change position often so that the tetracycline is distributed around the pleural space. The tube is then unclamped and free drainage permitted. If treatment with tetracycline fails or there are difficulties with intercostal intubation, C. parvum may be used as an alternative. C. parvum 7 mg diluted in 20 ml saline is injected into the pleural cavity.

III. ***Management of the fluid itself*** – Certain disadvantages may result from allowing the fluid to remain in the pleural cavity for any length of time – fibrin is deposited, the pleurae become thickened, re-expansion of the lung is hampered and the process may eventually lead to immobility of the thorax with loss of functional efficiency (frozen chest).

Therapeutic Thoracentesis

See Table 82.

PROCEDURE – *Position of patient* – The patient sits up against a back-rest or leans forward resting the arms on the top of a bed-table. *Site* – The skin is sterilized at the site of puncture which is usually the seventh or eighth intercostal

Table 77: Causes of acute pleural effusion

- Acute pancreatitis.
- Traumatic.
- Rupture of amoebic abscess into pleural cavity.
- Pulmonary infarction.
- Aortic dissection leak into pleural cavity.
- Oesophageal rupture.

Table 79: Bilateral pleural effusion

- Tuberculosis
- Infections: Viral, fungal
- Rheumatoid disease
- SLE
- Asbestosis
- Amoebiasis (Pleuropulmonary)
- Drug-induced
- Peritoneal dialysis.

Table 81: Predominant left sided fluid

- Acute pancreatitis
- Oesophageal rupture
- Dressler's syndrome

Table 78: Diseases producing both transudate and exudate

- Amoebic liver abscess
- Systemic lupus erythematosus
- Hypothyroidism
- Congestive heart failure.

Table 80: Predominant right sided effusion

- Amoebic liver abscess
- Congestive heart failure
- Liver cirrhosis
- Meigs' syndrome

Table 82: Indications for aspiration of fluid

- Large effusion upto clavicle.
- Cardiac or respiratory embarrassment.
- Bilateral effusion.
- Acute pulmonary oedema.
- Secondary infection of effusion.
- Persistence of fever and constitutional symptoms.
- If effusion does not tend to get absorbed spontaneously even when anti-tuberculous treatment is being given.
- Fluid is haemorrhagic or has high content of protein.

space in the mid-axillary line. Two percent lignocaine is used for local anaesthesia and it is injected right up to the parietal pleura. *Aspiration* – The aspiration needle is then introduced at right angles to the skin midway between two ribs and advanced into the chest till the penetration of the parietal pleura is indicated by a 'give in'. The needle is now attached to a 50 mL syringe with a two-way stop cork. As a rule not more than 1000 to 1500 mL of the fluid should be removed at one time. Aspiration should be discontinued if patient begins to cough or complains of tightness in the chest. After aspiration the needle is removed and the puncture wound sealed with collodion. If necessary aspiration may be repeated after 2 or 3 days.

Complications

1. *High negative intrapleural pressure* – The lung is unable to expand fully as indicated by increased pull on the syringe plunger. Patient feels tightness in the chest accompanied by coughing. This can be reduced by allowing some air to be sucked into the pleural space.
2. *Pleural shock* – due to vagal inhibition. The patient's head should be placed low and injection of adrenaline or dopamine given and oxygen started.
3. *Air embolism* – (a) If the aspiration needle tears the pleura and a superficial vein, air can be sucked into the pulmonary venous system through the needle itself or adjacent lung alveoli. (b) Air may enter the coronary arteries causing cardiac arrest. (c) More often air goes to the cerebral arteries and produces transient neurological symptoms and signs. Emergency treatment is to tilt the patient's head down with his right side uppermost to discourage air from entering these vessels.
4. *Pulmonary oedema* – If the fluid is removed too quickly, oedema may develop in the re-expanded lung tissue. Treatment is reduction of intrapleural pressure by allowing some air to be sucked into the pleural space.
5. *Circulatory collapse* – due to non-expansion of lung from pleural fibrosis causing high negative intrapleural pressure interfering with venous filling.
6. *Rupture of intercostal vessel* – rare.
7. *Pneumothorax or haemoptysis* – if lung is punctured.
8. *Empyema* – due to introduction of infection into the pleural space.

IV. ***Corticosteroids***– can help to achieve a more rapid absorption of the fluid thus reducing the risk of pleural thickening with loss of respiratory function. Prednisolone 10 mg b.d. or t.d.s. later reduced to 5 mg together with chemotherapy. It should be given for at least 6 weeks after the fluid is absorbed to avoid recurrence. Indications – (a) Patients with large effusions who are acutely ill. (b) If aspiration presents practical difficulties, or if loculation of fluid has occurred.

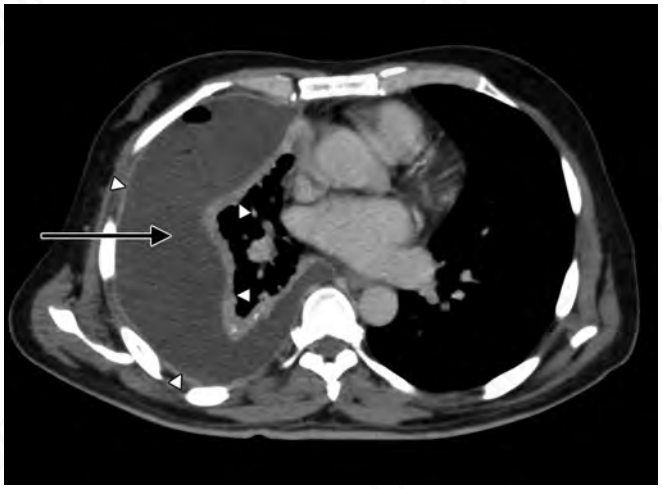


Fig. 67: CECT chest showing empyema with split pleura sign

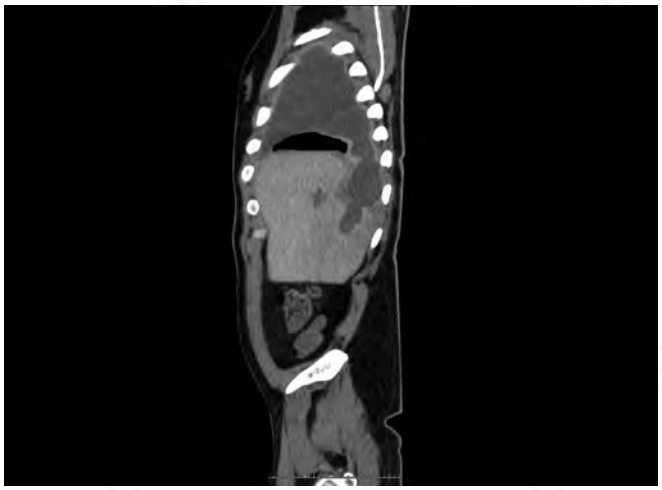


Fig. 68: CECT chest showing liver abscess tracking as empyema

V. ***Exercises***– to encourage expansion of the lower chest can be recommended quite early in the course of treatment.

EMPYEMA

Acute Empyema

Causes: See table classification of pleural fluids Table 77 to 81.

Symptoms

1. *Those of primary disease* – Imperfect recovery in pneumonic cases, or sudden increase in fever perhaps with rigors.
2. *Those due to mechanical effect* – Pleuritic chest pain in early stage, dyspnoea, cough and sputum.
3. *Those due to toxaemia*– Malaise, anorexia, sweats and loss of weight.

Signs

a. Same as effusion with sometimes oedema of chest wall.
b. Finger clubbing may develop within 2–3 weeks of the onset.

Investigations

Chest radiograph – Uniform opacity free in pleural space or localized by adhesions. Fluid level if bronchopleural fistula.

Leucocyte count – 15,000–20,000 per cmm.

Culture of fluid – for causative organism. Lack of bacterial growth suggests tuberculosis.

CT scan - (Figs 67 and 68)

Complications

1. *Bronchopleural fistula* – Expectoration of large volumes of purulent sputum which may be blood-stained. X-ray shows fluid levels.
2. *Empyema necessitans* – Untreated, an empyema may present as an abscess of the chest wall commonly in relation to costochondral junction of the rib.
3. *Pyopneumothorax* – Particularly empyema due to staphylococcal infection.

Management

Objectives of therapy – Control of infection, evacuation of pus, obliteration of pleural space, re-expansion of lung, and restoration of normal pulmonary function.

1. *Aspiration* – Pus is usually thin and should be aspirated with syringe every second or third day. Continuous drainage to a water seal may be necessary if fluid reaccumulates very rapidly.
2. *Antibiotics* – Penicillin 1 million units 6-hourly IM. Also intrapleurally 500,000 units at each aspiration in 5 to 10 mL of normal saline. If organism insensitive to penicillin other suitable broad spectrum antibiotic and metronidazole 400 mg t.d.s.
3. *Intercostal drainage* – if no definite improvement after about 10 days and in severely ill children. Indications for removal of drainage tube – (a) No fever suggesting control of infection. (b) Less than 100 mL fluid drainage in 24 hours. (c) Complete lung expansion. (d) Bronchopleural fistula if present, gets closed.
4. *Breathing exercises* – as soon as signs of general toxicity disappear.

Chronic Empyema

Empyema of more than 3 months duration is considered chronic.

Diagnostic criteria – (a) Demonstration of presence of bacteria in pleural space by culture and/or staining. (b) Culture negative pleural fluid with pH < 7 and glucose content < 40 mg/dL.

Causes

- *Ineffective drainage* – or failure to diagnose acute empyema.
- *Chronic infection* – Tuberculosis, lung abscess, bronchiectasis, actinomycosis.
- *Carcinoma lung* – with pleural involvement.
- *Bronchopleural fistula* – due to lung abscess, lung trauma or rupture of infected lung cysts.
- *Foreign body* – in pleural cavity, e.g. drainage tube, rib sequestrum.
- *Inadequate drainage of subphrenic abscess.*

Symptoms and Signs

Recurrent symptoms of chest pain and fever. Loss of weight and anaemia. Clubbing of fingers. Chest wall deformity from fibrosis. Chronic sinus tracts into the skin or lungs may develop. When bronchopleural fistula is present, air can be heard (or felt) blowing through a patent sinus during coughing.

Chest radiograph – Dense pleural opacity, crowding of ribs and elevation of diaphragm on affected side (Fig. 69).

Management

Intercostal drainage with instillation of appropriate antibiotics, streptokinase or rib resection and open drainage. When this fails, thoracotomy with excision of empyema sac, allowing the lung to re-expand and obliterate the dead space.

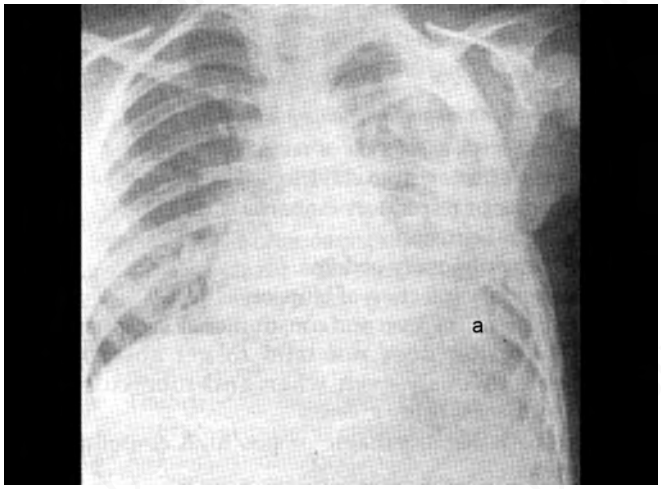


Fig. 69: Encapsulated empyema

27. THERAPEUTIC AEROSOLS

Successful inhalation therapy depends not only on choosing the correct drug, but also in delivering the drug in adequate amounts to the airways by use of an appropriate delivery system.

INDICATIONS AND MEDICATIONS FOR INHALATION DELIVERY

Asthma and COPD

- Bronchodilatation – β-agonists, anticholinergics
- Prophylactic therapy – Corticosteroids, cromoglycate
- Emergency therapy for acute asthma and COPD
- Expectoration – Saline

Cystic fibrosis

- Prevention/treatment of infection – Inhaled antibiotics
- Reduction of sputum viscosity – DNase
- Secretion hydration – Amiloride
- Protease inhibition – α_1- antitrypsin
- Gene therapy – via liposomes or viruses

AIDS

- Prevention of *Pneumocystis jiroveci* pneumonia – Inhaled pentamidine
- Palliative care
  Intractable cough – Lignocaine (probably)
- Treatment of hyperkalaemia

Nebulized salbutamol is as effective as i.v. insulin and glucose in reducing plasma potassium levels in uraemia

Immunization

- Measles vaccination – High rates of seroconversion in young infants vaccinated by inhalation route
- Treatment of croup
- Reduction of inflammation – Adrenaline and corticosteroids

Inhalational drug delivery in intensive care

- ARDS – Surfactant, prostacyclin, nitric oxide related vasodilators.
- Pulmonary hypertension – Nitroprusside, $MgSO_4$
- Bronchopulmonary dysplasia – Corticosteroids.

DEVICES FOR INHALING MEDICATIONS

Pressurised Metered Dose Inhalers (PMDIs) – are most widely used devices in treatment of airflow obstruction because of small size, convenience and low cost.

Chlorofluorocarbons – Free corticosteroid MDIs deliver a finer aerosol, with higher lung delivery and more peripheral deposition

Spacehaler – is a specially adapted MDI actuator that slows the emitted aerosol cloud, reducing oropharyngeal deposition of the drug and enhancing lung delivery.

Spacer devices – are used to improve therapy in specific group of patients, or to increase the proportion of delivered drug deposited in the lungs. Routine use of spacer devices with inhaled corticosteroids reduces the incidence of oral candidosis and dysphonia and decreases adrenal suppression.

Spacer devices may be divided into three broad types – (i) Simple 'tube spacer' extensions to the inhaler mouthpiece. (ii) Holding chambers, which generally have a one-way inhalation valve at the mouthpiece. (iii) 'Reverse flow' devices with the MDI being fired in a direction 180 degrees from the mouth, either into a collapsible bag, or into small volume from which outside air is entrained.

Dry powder inhalers (DPIs) – Rotahaler – The capsule containing the powder inhaler is inserted into the end of the device and broken up by twisting the mouthpiece. The powder falls into the body of the inhaler and the patient has to inhale through the mouthpiece to disperse the powder and to deliver the micronised drug particles to the lung.

Nebulizers – are useful for patients unable to use other devices, and for infants. Jet nebulizers are powered by compressed air (usually from an electrically operated compressor) by which compressed air passing through a constriction (venturi) undergoes a small reduction in pressure; this causes drug solution to be drawn up from a reservoir and fragmented into droplets in the gas stream. Nebulizers are a convenient way of delivering large doses of bronchodilators that may be required in treatment of acute severe asthma. Nebulizers have significant merit in terms of flexibility, i.e. a spray can be made of any drug substance and in virtually any dose.

28. DRUGS AND THE LUNGS

Undesired effects on the lungs from drugs can be:

1. INDIRECT – e.g. worsening of respiratory failure by sedative, haemoptysis from anticoagulants, or paralysis of respiratory muscles from muscle relaxants.
2. DIRECT – by toxic or immunological mechanisms –

A. Airways reactions:

a. ***Drug-induced asthma*** –
   Effect predictable on pharmacological basis –
   β-blockers
   Cholinergic agents (pilocarpine, carbachol)
   Cholinesterase inhibitors (pyridostigmine)
   Unpredictable or idiosyncratic reactions – Oral: Analgesic and anti-inflammatory drugs. Parenteral: Penicillin, aminophylline, iron-dextran complex, hydrocortisone, N-acetylcysteine.

b. ***Drug-induced cough*** – ACE inhibitors, due to increased concentration of kinins (Normally ACE catalyses the degradation of these peptides.

B. Alveolar reactions:

a. ***Noncardiogenic oedema* or *ARDS*** – Opiates or salicylates overdose, hydrochlorothiazide, β-sympathomimetic agent, e.g. isoxuprine, naloxone, cytosine arabinoside.

b. ***Eosinophilic reaction***– Inflammatory exudative alveolitis with excess eosinophils in tissues and blood. Clinical picture varies from transient radiographic infiltrate to life-threatening illness with respiratory distress and hypoxemia. Often associated maculopapular rash. Common agents are sulphonamides, antibiotics like penicillin and tetracycline, neuroleptic agents, methotrexate and procarbazine.

c. ***Alveolitis and/or fibrosis*** – Gradual onset of progressive shortness of breath, dry cough and sometimes fever. Chest X-ray shows non-specific interstitial or alveolar shadowing. Causes: Cytotoxic agents, e.g. bleomycin, busulphan. Other agents include oxygen, nitrofurantoin, amiodarone, tocainide.

C. Pleural reactions:

Pleural effusion or thickening. (i) *Drug-induced lupus syndrome* (procainamide and hydralazine in large doses). Amiodarone, Nitrofurantoin, Phenytoin, Methotrexate. Also at times Carbamazepine, Penicillamine, Cyclophosphamide. (ii) *Pleural reaction only* – Pleural fibrosis (often associated with retroperitoneal and mediastinal fibrosis) –Methysergide, methotrexate, bromocriptine, dantrolene.

29. RESPIRATORY PROBLEMS IN IMMUNOSUPPRESSED PATIENTS

Table 83 explains the infectious disorders, non infectious disorders and Iatrogenic diseases in Immunosuppressed Patients and Table 84 gives differential diagnosis of fever with pulmonary infiltration in an immunocompromised patient based on chest X-rays and onset of symptoms.

30. LUNG TRANSPLANTATION

INDICATIONS

Chronic Airflow Limitation

- COPD (often α_1-trypsin deficiency)
- Chronic asthma with fixed obstruction
- Bronchiolitis obliterans

Suppurative Lung Diseases

- Cystic fibrosis
- Bilateral bronchiectasis of other cause

Pulmonary Vascular Disease

- Primary pulmonary hypertension
- Eisenmenger's syndrome
- Thromboembolic pulmonary hypertension

Interstitial Lung Disease

- Cryptogenic fibrosing alveolitis

Uncommon Indications

- Severe chronic fibrotic sarcoid
- Severe chronic hypersensitivity pneumonitis
- Pulmonary lymphangioleiomyomatosis
- Histiocytosis X
- Re-transplantation
- Bronchoalveolar cell carcinoma

Table 83: Respiratory problems in immunosuppressed patients

Infectious Disorders	
Neutropenia	Gram-ve bacteria Staph. aureus Aspergillus and other mycelial fungi
Immunoglobulin deficiency	Strep. pneumoniae H.influenzae Mycoplasma
T lymphocyte deficiency	Bacterial infection as above Pneumocystis jiroveci and other fungi Mycobacterium Herpes viruses (CMV, varicella zoster) Nocardia asteroides Toxoplasma gondii
Non-infectious disorders	
• Pulmonary oedema	
• Pulmonary hemorrhage	
• Pulmonary embolism	
• Tumour (solid tumour, lymphoma/leukaemia, Kaposi's sarcoma)	
• Alveolar proteinosis	
Iatrogenic	
• Drug (pneumonitis)	
• Radiation (pneumonitis)	
• WBC transfusion (leucoagglutinin reaction).	

SELECTION OF ORGAN DONORS

- Brain death
- Exclusion of HIV-positive and hepatitis B antigen positive donors
- Adequate gas exchange (PaO_2 > 300 mm Hg at 100% FiO_2 and 5 cm H_2O positive end-expiratory pressure)
- Absence of significant pulmonary pathology on chest radiograph or bronchoscopy
- No significant active infection, or recent history of malignancy

TYPES OF LUNG TRANSPLANTATION

• Single lung	Interstitial pulmonary fibrosis
• Double lung	Suppurative conditions (e.g. cystic fibrosis) Pulmonary vascular disease Bilateral severe bullous emphysema
• Heart - lung	Pulmonary hypertension with irreversible uncorrectable cardiac abnormality

COMPLICATIONS AFTER LUNG TRANSPLANTATION

• Hyperacute rejection	Seconds to minutes
• Pulmonary oedema	
• Bacterial lower respiratory tract infection	12–72 hours
Donor - acquired	Hours to days
Recipient - acquired	Days to years
• Airway complications	Week to 1 month

Table 84: Differential diagnosis of fever with pulmonary infiltration

Chest X-ray	*Acute onset*	*Subacute or chronic onset*
1. Consolidation	Bacterial	Fungal
2. Interstitial infiltrate	Thromboembolic	Nocardial
3. Nodular infiltrates	Pulmonary haemorrhage	Tuberculous
	Pulmonary oedema	Viral
	Leucoagglutinin reaction (Acute lung injury following transfusion)	Viral Pneumocystis jiroveci Radiation pneumonitis Drug – induced Tumour
	Bacterial	Fungal
	Pulmonary oedema	Nocardial Tuberculous Sarcoidosis

- Acute rejection — Week to 2 years
- Opportunistic infections — Week to 4 years
- Chronic rejection (including bronchiolitis obliterans) — Week to 6 years

31. MISCELLANEOUS

Yellow nail syndrome – Effusions associated with yellow discolouration of nails, lymphoedema and occasionally bronchiectasis and sinusitis. Lymphatic hypoplasia is the underlying disorder and the likely mechanism for the effusion.

Silhouette sign. The outline of many structures on the chest X-ray is visible because of an interface between opaque tissue (heart or diaphragm) and air in the lungs. If the lung adjacent to such structures also becomes opaque the 'silhouette' is lost. Thus collapse of the left lower lobe obscures the left hemidiaphragm and collapse of the lingula or right middle lobe obscures the left and right heart borders.

Bronchopleural fistula: Causes

- Lung abscess — Traumatic chest injury
- Cavity (Tuberculosis) — Post lung resection
- Necrotising pneumonia — Barotrauma

STEM CELLS AND LUNG DISEASES

Therapeutic Potential of Stem Cells

1. ARDS (regeneration of extracellular matrix)
2. Emphysema (regeneration of alveoli and extracellular matrix)
3. Lung fibrosis (regeneration of extracellular matrix)
4. Cystic fibrosis (stem cells acting as genetic vectors)
5. Pulmonary arterial hypertension (Endothelial progenitor cells transducted with nitric oxide synthetase)
6. Lung cancer (targeting endogenous stem cells with potential for malignant transformation by identifying with specific surface markers).

CHAPTER

The Cardiovascular System

4

1. INVESTIGATIONS IN CARDIOVASCULAR DISEASES

BLOOD

Full blood count, measurement of serum electrolytes and urea, uric acid, serum lipids, homocysteine. Thyroid function tests.

CHEST RADIOGRAPH

The structures to be observed are:

- The heart for size, chamber enlargement, valvular and other calcification.
- Lungs for pulmonary venous hypertension and pulmonary ossification.
- Mediastinum for aorta, superior vena cava, pulmonary arteries and veins.
- Thorax for depressed sternum and rib notching.

ELECTROCARDIOGRAM

The ECG is useful when:

- Patient has symptoms which suggest heart disease.
- Cardiac rhythm is irregular.
- In presence of cardiac enlargement.
- Heart murmurs are heard or heart failure is present.
- Exercise testing is useful in diagnosis of ischaemic heart disease.

HOLTER MONITORING

The equipment is a battery-powered recorder which samples ECG data comparable to data recorded by leads V1 and V5. These recorders allow for 24 hours continuous monitoring.

Clinical Uses

- To diagnose arrhythmias
- Assess antiarrhythmic therapy
- Assess pacemaker or implanted cardioverter defibrillator (ICD) function
- Detect ischaemia
- Monitor BP (using appropriate transducer)
- Determine prognosis

TREAD MILL TEST (TMT) ECG

Patients presenting for exercise testing may be divided roughly into subgroups:

- Those able to exercise maximally with an uninterpretable ECG.
- Those unable to exercise or can exercise only submaximally.
- Those with an uninterpretable ECG (due to LVH, LBBB, digitalis effect, etc.).

Indications

1. *Ischaemic heart disease:* (a) Diagnosis. (b) Risk stratification. (c) Assessment of suitability for and assessment of exercise training and rehabilitation. (d) Follow-up of patients with known CAD. (e) Screening asymptomatic men >40 years of age who are in specific professions (pilots, firemen, vocational drivers).
2. *Acute myocardial infarction:* Risk stratification and assessment of exercise tolerance.
3. *Coronary angioplasty or bypass grafting:* (a) Reassessment of recurring symptoms. (b) Routine evaluation pre- and post-intervention – (i) Early: 2–7 days after PTCA, 6 weeks after CABG. (ii) Late: 6 months after PTCA or CABG.
4. *Heart failure:* (a) Diagnosis of underlying cause (e.g. ischaemia). (b) Evaluation of symptoms in relation to exercise capacity. (c) Assessment of the need and timing of cardiac transplantation.
5. *Arrhythmias:* (a) Diagnosis in patients with exercise-related palpitations, dizziness or syncope. (b) Pacemaker selection in chronic A-V block.

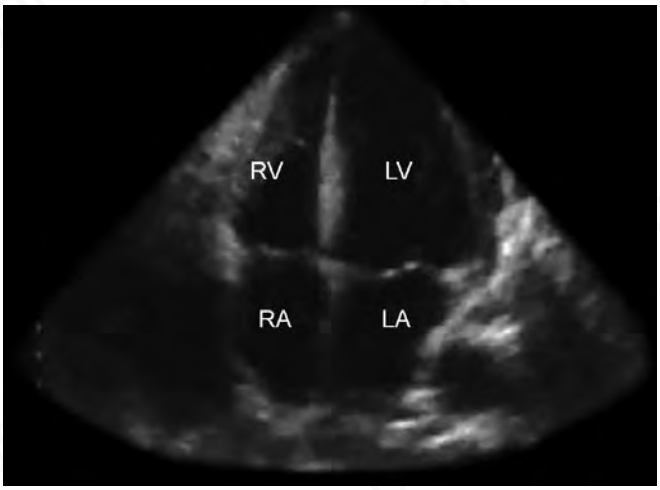


Fig. 1: 2D echo apical 4 chamber view showing normal heart

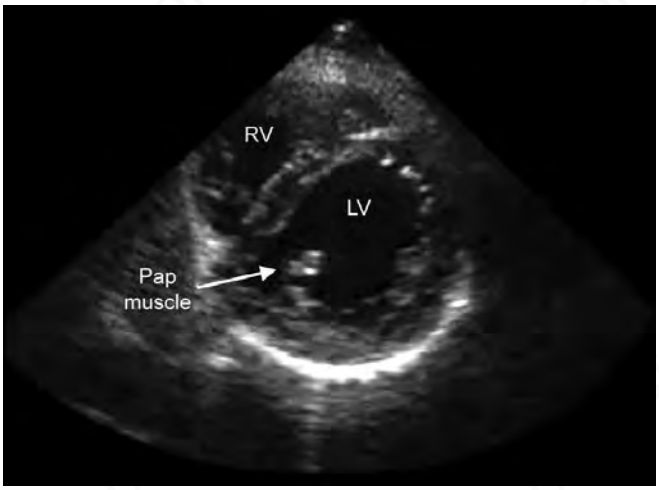


Fig. 2: 2D echo parasternal short axis view showing normal heart

Criteria for Positive TMT

- *Mildly positive*: Horizontal ST depression of 1 to 5.5 mm and slowly rising junctional depression which remains depressed 1.5 mm more than 80 mins after the J point.
- *Moderately positive:* Horizontal ST depression of 1.5 to 2.5 mm, slowly rising ST depression which remains depressed more than 2.5 mm 80 mins after the J point and down sloping ST depression with J point depressed 1.2 mm.
- *Strongly positive:* Flat ST depression 2.5 mm or more, slowly rising ST depression at J point of 2 mm or more and horizontal sloping ST depression appearing in first stage of the exercise and remaining depressed for more than 8 mins into recovery.

ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND

The heart can be imaged with reflected ultrasound by the complimentary techniques of M-mode and cross-sectional echocardiography (CSE). Both techniques depend on high frequency sound which is transmitted to and then reflected from intracardiac structures. These echoes from the heart are then converted electronically into an image of the structures that reflected the sound waves.

Cross-sectional Echocardiography (CSE or 2D Echo)

Here multiple ultrasound beams, each produced by a single ultrasound crystal or by mechanically scanning the heart with a single crystal create a sector-shaped cross-section of the heart. Between 30 and 50 such cross-sections are built up per minute and presented as a moving picture. Imaging planes such as parasternal, apical or subxiphoid are used to produce a complete picture of the heart. While 2D echocardiography does provide an accurate method for assessment of LV function, systolic 3D provides an accuracy in the assessment of LV volumes, and can be compared with gold standards such as cardiac MRI or radionuclide volumes (Figs. 1 to 3).

3D Echocardiography

(a) Assessment of ventricular function. 3D echo provides greater reproducibility, reliability and accuracy than 2D echocardiography in assessment of LV volumes and EF compared with cardiac MRI or radionuclide volumes. Global as well as regional wall motion can be displayed parametrically. (b) Congenital heart disease—3D echo is useful in assessment of congenital cardiac lesions. (c) LV dyssynchrony—3D echo can simultaneously integrate the clinical effects of radial, circumferential and longitudinal effects of all 17 myocardial segments on cardiac dyssynchrony.

Table 1 gives various modalities of echocardiography and their uses.

Transthoracic Echocardiography

Indications: See Table 2.

Transesophageal Echocardiography (TOE)

By mounting both imaging and Doppler transducers on a gastroscope, the heart can be interrogated from the oesophagus. Since there is little tissue between the heart and the transducer, high quality pictures can be obtained.

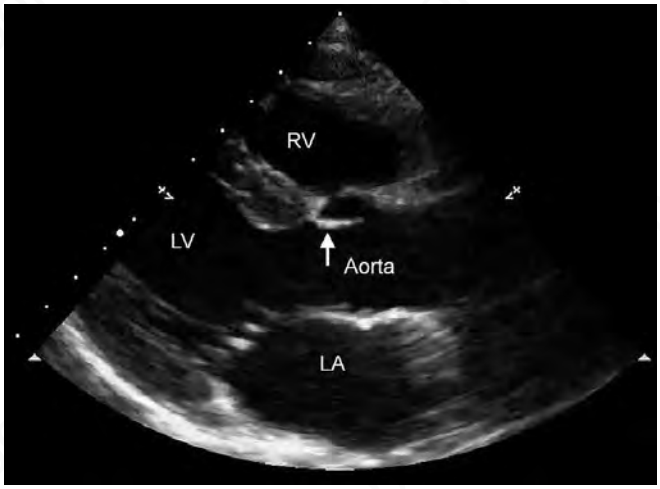


Fig. 3: 2D echo parasternal long axis view, normal heart, arrow shows aortic valve

Advantages – (a) Excellent access and superior imaging. (b) Valves closer to transducer, hence vegetations, prosthetic valve function more easily seen. (c) Clear vision of ascending and descending aorta.

Indications for Transesophageal echocardiography (with preparatory transthoracic study) are given in Table 3.

Stress Echocardiography

Stress echocardiography is used to predict presence of coronary disease, to stratify the risk of a coronary event and to detect hibernation. It is also used for assessment of functional reserve in patients with end-stage valve disease (Table 4).

Echocardiography in Suspected Heart Failure

Indications:

- Breathlessness or dependent oedema and clinical findings that suggest or cannot exclude heart disease
- Unexplained hypotension
- Exposure to cardiotoxic agents
- Known cardiomyopathy where there is a change in cardiac status

Echocardiography in Valve Disease

Indications for echocardiography in valvular heart disease are listed in Table 5.

Echocardiography for Screening

- Family history of genetically transmitted cardiovascular disease, e.g. Marfan syndrome, hypertrophic cardiomyopathy, dilated cardiomyopathy
- Potential donors for cardiac transplantation
- Baseline and re-evaluation of patients undergoing chemotherapy with cardiotoxic agents

Table 1: Modalities of echocardiography and their uses

Two-dimensional imaging	To describe anatomy and motion To measure cavity size and wall thickness To measure LV outflow tract diameter for calculation of stroke volume To estimate LV volumes and ejection fraction Planimetry of the orifice of mitral valve in mitral stenosis
M-mode	Measurement of cavity size and wall thickness Estimation of LV mass Timing of events within the heart In combination with colour flow mapping aids timing of a flow pattern
Continuous wave Doppler	Calculates the grade of stenotic valve lesions Estimates pulmonary artery pressure Semiquantitative assessment of the grade of valve regurgitation
Pulsed Doppler	Assesses diastolic LV function from recording at the mitral valve and in a pulmonary vein Estimates orifice area of aortic valve (in combination with 2D imaging and continuous wave Doppler) Calculates stroke volume and cardiac output Estimates shunt size
Colour flow mapping	Screens for abnormal flow, e.g. valve regurgitation or a shunt Semiquantitative estimate of grade of valve regurgitation
Doppler tissue	Detecting asynchrony of imaging contraction, e.g. early depolarization in Wolff-Parkinson-White syndrome or the origin of ventricular tachycardia Describing diastolic and systolic function including time intervals, regional function, long axis function and differences between endocardial and epicardial function. These can be used for diagnosis of coronary disease at rest or during dobutamine stress

CARDIAC CT

Demonstrates whether the coronary tree is normal or abnormal. Also, if the test is abnormal, it can tell the extent of abnormality which can range from minor disease (calcified, non-calcified plaques), to severe stenosis and occlusions.

Indications for Cardiac CT to rule out CAD—(a) Family H/o CAD (b) Atypical chest pain. (c) Preadult congenital heart disease or cardiac tumour surgery. (d) Pre-major surgery in adults over age of 50. (e) Smoking. (f) Equivocal ECGs, echocardiograms or after stress studies as routine check-up.

MAGNETIC RESONANCE IMAGING (MRI)

Is a powerful tool providing high-resolution images of the heart and great vessels without the use of ionising radiation or contrast agents.

Table 2: Indications for echocardiography

- *Congenital heart disease.*
- *Ischaemic heart disease*
  - (a) Diagnosis of acute chest pain.
  - (b) Stress echocardiography.
  - (c) Complications of MI.
  - (d) Detection of viable myocardium.
- *Heart failure*
  - (a) Diagnosis of mechanism, e.g. predominant systolic or diastolic dysfunction, dilated cardiomyopathy vs. restrictive heart muscle disease.
  - (b) Diagnosis of cause, e.g. IHD, unsuspected AS.
  - (c) Estimation of ventricular filling pressures.
  - (d) Assessment of global LV function and prognosis.
- *LV hypertrophy.*
- *Hypertrophic cardiomyopathy.*
- *Pericardial effusion and constriction.*
- *Valvular heart disease*
  - (a) Diagnosis and quantitation of valve stenosis or regurgitation.
  - (b) Mitral valve prolapse.
  - (c) Infective endocarditis.
  - (d) Monitoring function of prosthetic heart valves.
- *Suspected cardiogenic embolism or intracardiac thrombus* (in conjunction with TOE).
- *Suspected cardiac tumour*, e.g. myxoma.
- *Miscellaneous*
  - (a) Foetal echo when obstetric surveillance suggests a possible cardiac problem.
  - (b) Neonatal with cyanotic CHD.
  - (c) Older children: To exclude significant disease in patients with innocent systolic murmurs.
  - (d) Adult survivors of surgery for complex CHD developing problems.

Table 3: Indications for transesophageal echocardiography

Suspected endocarditis
• In all cases of prosthetic valve endocarditis
• If transthoracic study is nondiagnostic
• Consider in all cases of native endocarditis
Cerebral infarction, TIA, peripheral embolism
• Patients aged <50 years with cerebral infarction
• Patients aged >50 years without evidence of cerebrovascular disease or other obvious cause, in whom the findings of echocardiography will change management (e.g. to start warfarin if a patent foramen ovale is found)
Prosthetic valve
• If patient is unwell, even if the transthoracic study is normal
• To improve quantification of MR
• Suspected endocarditis
Native valve disease
• To determine feasibility and safety of balloon mitral valvotomy
• To determine whether some cases of MR are repairable
Atrial septal defect
• To determine whether percutaneous closure is possible
Aorta
• To diagnose dissection, intramural hematoma
• To determine the size of the aorta if not clear transthoracically
Intraoperative
• To monitor left ventricular function
• To assess de-airing of the heart after cardiac surgery
• To assess the result of valve repair
Intensive care unit
• To assess loading, LV and RV function and valve function

Indications

- **Left ventricular structure and function:** Gradient echo sine imaging can provide multiple frames in a single slice with good contrast between myocardium and blood, and is accurate in measuring LV volumes. Wall thickening more accurately reflects extent of myocardial dysfunction in ischaemic heart disease than does wall motion. Using sine MRI, wall thicke-ning can be quantified.
- **Valvular function:** Cine MRI can be used for identification and qualitative assessment of the severity of regurgitant or stenotic valvular lesions. Velocity encoded (VEC) MRI can be used to calculate velocity of blood flow through a given plane.
- **Pericardial disease:** MRI allows differentiation of tissue characteristics. For example haemorrhagic, serous and chylous pericardial effusions can be differentiated based on their signal properties (T_1 or T_2-weighted sequences).

  MRI is a sensitive measure of pericardial thickness in constrictive pericarditis.
- **Aortic disease:** MRI can provide evaluation of the aorta and its branch vessels. MRI is nearly 100% sensitive in diagnosis of aortic dissection. Gadolinium-DTPA enhanced three-dimensional MRI angiography helps in diagnosis of congenital aortic disease (Fig. 4), aortic aneurysms and dissection.
- **Congenital heart disease:** 3D displays allow measurement of LV volumes and mass and shunt calculations can be performed with phase velocity mapping of flow in ascending aorta and main pulmonary artery.
- **Cardiac masses:** Evaluation of intra and extra cardiac masses and intracardiac thrombi. Cine MRI for describing the attachment and motion of cardiac masses (Fig. 5).

Table 4: Indications of stress echocardiography
• Clinical uncertainty and normal or equivocal conventional exercise test
• Patient unable to exercise
• Resting ECG precluding electrical analysis (e.g. LBBB, LV hypertrophy with strain, digoxin)
• Risk stratification after acute MI
• Need to localize site of ischaemia
• To assess functional significance of a coronary stenosis in planning angioplasty or surgery
• To detect hibernating myocardium
• To grade aortic stenosis in presence of a low LV ejection fraction
• To determine if MR develops or worsens during strain

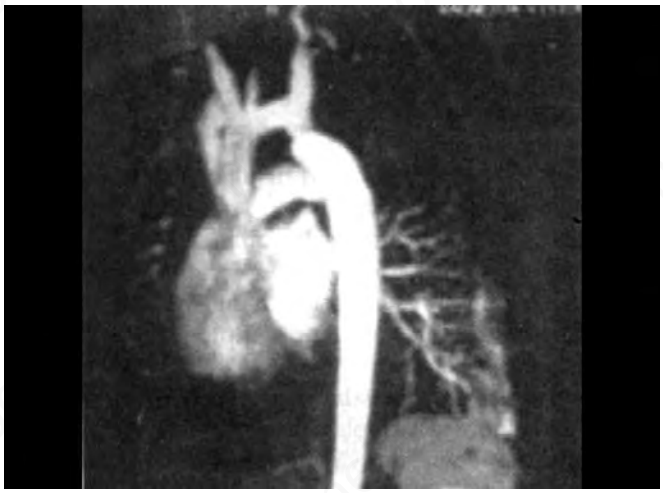


Fig. 4: A 3D Gd-DTPA - enhanced MR angiogram of a 3-year-old patient with a significant coarctation of the descending aorta just distal to the subclavian artery

- **Anomalous coronary arteries:** 2D MRI angiographic approaches to identify the course of anomalous coronary arteries.
- **Arrhythmogenic RV cardiomyopathy:** MR signs of this disorder include fatty infiltration of RV free wall, wall thinning, systolic dysfunction and cavity dilation.
- **Ischaemic heart disease**
- *Pharmacologic stress testing.* Dobutamine stress cine MRI shows improved sensitivity and specificity compared to dobutamine echocardiography.
- *Perfusion.* Gd-PTA based contrast agents can be infused to assess myocardial perfusion in myocardial ischaemia.
- *Contrast-enhanced infarct detection.* Using an imaging sequence, delayed hyper enhancement seen 5–15 minutes after contrast infusion delineates infarcted tissue.

Carotid intima-medial thickness (CMT) has a correlation with coronary risk factors. A high carotid IMT is a surrogate and reliable marker of higher risk of CAD. The carotid intima-medial thickness is measured by duplex screening of carotid arteries (use of Doppler to estimate blood flow characteristic in conjunction with B-mode ultrasound) is one of the most reliable markers for atherosclerotic vascular changes.

Table 5: Indications of echocardiography in valve disease
• If patient is previously uninvestigated and symptomatic disease
• Murmur suggesting a moderate probability of organic disease
• Ejection systolic murmur filling most of systole or any pansystolic murmur
• Any diastolic murmur
• Abnormal second heart sound
• Wide pulse pressure and displaced apex beat or enlarged cardiac shadow
• Re-evaluation if there is LV dilation even if valve disease is mild or moderate
• Re-evaluation if symptoms change or with severe valve disease even with no symptoms
• Evidence of endocarditis
• Known significant valve disease and pregnancy
• For planning valve replacement, repair or valvotomy
• Routinely soon after valve surgery or if symptoms or signs suggest dysfunction

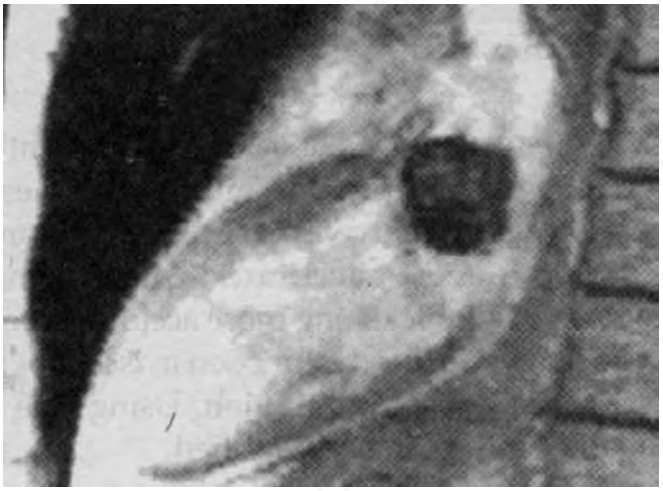


Fig. 5: Parasagittal 2-chamber long axis T1-weighted gradient echo cine image of a large left atrial myxoma (large round mass with low signal intensity) attached to the superior pole of the left atrium and prolapsing across the mitral valve

Myocardial viability – In patients who have already infarcted, it is necessary to know whether there is enough viable myocardium available, prior to attempting revascularization. If the myocardium is nonviable, there is no point doing a bypass or stenting the affected artery.

- **Cardiomyopathies –** (a) *In dilated cardiomyopathy,* cardiac MRI show global hypokinesia in absence of infarction and mid-myocardial fibrosis in a few cases. (b) *Hypertrophic cardiomyopathy* – Cardiac MRI is the most sensitive modality to assess the presence of apical HCM, which is often missed on echocardiography. In HOCM, it allows one to assess the extent of myocardial fibrosis and damage as well as the subaortic stenosis and flow impairment. (c) *Inflammatory and infiltrative cardiomyopathies* – In patients who have abnormal ectopics or who present with supraventricular or right ventricular tachycardias, it is important to know whether there is a structural cause for this. CMR is the most sensitive tool for diagnosing myocardial pathology. Sarcoidosis is the commonest inflammatory condition to affect the heart and presents with abnormal focal areas of enhancement in the RV and LV with wall motion abnormalities. Often mediastinal and hilar lymphadenopathy is seen in same study.

Cine magnetic resonance angiography (MRA): Shows graft patency well and its accuracy is similar to CT without the need for contrast agents. MRA using phase contrast techniques allows noninvasive measurement of flow in bypass grafts.

Contraindications for MRI – Cardiac pacemaker, ferromagnetic cerebral aneurysm clip, cochlear implant.

Magnetic resonance contrast agents for cardiac imaging: While MRI allows study of cardiac anatomy and contractile function in detail, tissue characterization of the pathophysiologic state of the myocardium may require special indicators or MRI contrast agents. These extracellular, blood pool and intracellular agents provide a wide range of indicator properties, e.g. myocardial extracellular space, blood pool, capillary permeability and membrane transport. Combined use of MRI and MRI contrast agents can thus provide a single diagnostic examination that fully and quantitatively assesses all indices of cardiac performance.

Nuclear magnetic response spectroscopy (NMR) – This is useful for evaluation of changes in metabolism with different disease states, as well as with therapeutic interventions:

- Metabolic evidence of ischaemia in patients with myocardial infarction and patients with known coronary disease.
- Patients with dilated and hypertrophic cardiomyopathies often have phosphodiester resonance.
- Changes suggestive of heart transplant rejection.

NUCLEAR CARDIOLOGY

It is the study of cardiac function, myocardial perfusion and blood flow, myocardial metabolism and myocardial damage with radio-pharmaceuticals. The complementary nature of the functional and physiologic informations with the anatomic and structural information obtained from cardiac catheterization procedures has led to widespread application of these techniques.

Techniques

1. **Myocardial infarct imaging:**
   a. ***Technetium-99m labelled pyrophosphate*** is an infarct-avid agent that serves as a marker for post-necrotic inflammation. *Disadvantages:* Scans do not become positive until 12–24 hours after infarction, and it requires significant amount of transmural necrosis before a diagnostic 'hot spot' is detected. *Uses*–Patients with LBBB or who are permanently paced (because changes of infarct are masked in these cases), or where enzyme tests are equivocal.
   b. ***Indium-III labelled antimyosin:*** Advantage over pyrophosphate imaging is that its delivery does not depend on residual flow to the infarct. Also useful for detecting necrosis due to rejection episodes in transplanted heart and imaging acute myocarditis.
2. **Myocardial perfusion imaging:**
   a. ***Thallium-201 or Technetium-99m SESTAMIBI imaging*** – TI 201 when injected IV provides information regarding relative regional myocardial perfusion. Hypoperfused areas appear as image defects. Areas of infarction on a cardiac image will appear as fixed defects in resting perfusion scans.

   Stress thallium myocardial perfusion scanning: Patient is subjected to a symptom limited exercise on treadmill or bicycle ergometer. 2–3.5 mci Thallium is injected iv at peak exercise and exercise is continued for further one minute. Patient is then transferred to the imaging table and images of the myocardium taken in multiple views.

   In case of coronary artery stenosis, there is inhomogeneity of Thallium uptake with intense uptake in areas of myocardium supplied by normal arteries and relatively decreased uptake (perfusion defect) in areas supplied by stenosed arteries. Usually after about 4 hours, when the initial area of perfusion defect will show the same thallium concentration as the surrounding normal myocardium since thallium is washing in into ischaemic myocardium. Such a 'reversible perfusion defect' is the hallmark of ischaemic viable myocardium.

If the myocardium is infarcted, there will be no extraction of thallium in post-exercise images at 4 hours and then at 24 hours, the perfusion defect persists and is called 'fixed', or persistent defect indicating myocardial infarction.

b. **Positron Emission Tomography (PET)** – Radiopharmaceuticals can be used to label natural substrates of myocardial metabolism. The positron is a positively charged electron produced during decaying of a nucleus. After the positron reacts with neighbouring electron, a pair of electrons are emitted which move at a direction 180° apart. The principle of positron tomography is an array of imaging detectors positioned round the patient. Different positive emitters can be used to study blood flow, e.g. N-13 ammonia, glucose utilisation (F-18 deoxyglucose), and metabolism and myocardial oxygen consumption.

Uses of Myocardial Perfusion Imaging

See Table 6 for indications of myocardial perfusion imaging.

3. **Myocardial metabolism:** Single photon emission computed tomography (SPECT) imaging has superseded multiple view planar images. SPECT technique gives a three-dimensional view, and the exact site and size of the lesion can be more readily determined. Also, multivessel coronary disease can be clearly identified by separating the perfusion defects into separate vascular territories. 'Bull's-eye' imaging is a topographical representation of multiple sagittal sections of the myocardium stacked in two dimensions from the apical section in the centre to the larger basal segments in the outer ring; this technique gives a 'topographical' view of LV perfusion. SPECT SESTAMIBI imaging reduces the false-positive rate and improves specificity for detection of an individual coronary stenosis.

   Myocardial perfusion scanning with exercise: Myocardial imaging may be used to assess infarct size, myocardial viability, detection of multivessel disease and prognosis.

   Myocardial perfusion imaging with pharmacological 'stress': In patients unable to exercise, pharmacological 'stress' perfusion imaging is useful using SESTAMIBI or ^{99m}Tc-tetrofosmin.

Table 6: Indications of myocardial perfusion imaging

• Risk stratification in IHD.
• Management and follow-up after therapeutic interventions, e.g. coronary angioplasty or surgery
• Prognostic assessment
• Detection of myocardial viability in ischaemic LV dysfunction.

   a. Dipyridamole or adenosine is used to increase coronary blood flow. The 'differential' flow between the normal artery and stenotic artery produces a relative perfusion detect, which can be imaged by perfusion agents.

   b. *Dobutamine* is also used for evaluating CHD. Dobutamine infusion, 5–40 mg/kg/min, produces a significant increase in B.P. and heart rate, which may precipitate myocardial ischaemia in patients with CHD. Use of simultaneous two-dimensional echo-cardiography and ^{99m}Tc SESTAMIBI SPECT to assess myocardial perfusion during dobutamine stress has an extremely high sensitivity and specificity for detecting CHD.

4. **Ventricular function studies:** The procedure known as radionuclide angiocardiography (RNV) is used in the assessment of ventricular performance. Two methods are available:

   a. ***Equilibrium multigated technique (MUGA)*** involves labelling the blood pool with ^{99m}Tc tagged to the patient's own RBCs, and imaging the whole cardiac blood pool carried at equilibrium using the ECG to gate the cardiac cycle so that systole and diastole can be adequately resolved. The left anterior oblique view is obtained to provide separation between right and left ventricles.

   b. ***First-pass method*** measures right and left ventricular performance sequentially during the initial transit of a bolus of radiotracer through the right and left heart.

Clinical uses – MUGA and first-pass studies are useful for: (a) Detection of left ventricular aneurysms and the differentiation of aneurysms from diffusely hypokinetic ventricles as well as for general assessment of LV function. (b) Left and right ventricular ejection fractions can be measured accurately. (c) Cardiac volumes may also be produced from which ejection and relaxation indices can be derived.

CARDIAC CATHETERIZATION

It is an invasive procedure which can be performed for:

- *Measurement of* – (i) Intracardiac pressures. (ii) Intracardiac oxygen saturation. (iii) Cardiac output.
- *As part of:* (i) Angiography. (ii) Angioplasty. (iii) Valvuloplasty. (iv) Cardiac biopsy.

Indications

- *Valve disease:* Severity of AS or PS.
- *Heart muscle disease*–Both hypertrophic and dilated cardiomyopathy can be diagnosed by echo, and

cardiac catheterization can be only of benefit for the information provided by coronary angiography, or when cardiac biopsy is indicated.

- *Heart failure* – Right heart catheterization is very useful for monitoring response to treatment in acute heart failure.
- *Measurement of cardiac output* is of little value clinically but essential for measurement of pulmonary or systemic vascular resistance in management of shock or as part of the work-up for cardiac transplantation.
- *Congenital disease* – Catheterization is usually reserved for complex cases. A balloon catheter can be used to create an atrial septal defect in transposition of great vessels in which intracardiac shunt can preserve life.
- *Cardiac biopsy* – in patient with suspected cardiomyopathy.

Intracardiac Pressures

Pressures within the cardiovascular system rise and fall. The changes are converted into wave forms either by moving a recording paper under a stylus or by sweeping a spot across an oscilloscope (Table 7).

Techniques – (a) Pressure in right chambers of heart and pulmonary artery are obtained by advancing a catheter through a vein (antecubital or femoral). This can be performed under fluoroscopic control or a catheter with an inflatable balloon near its tip can be carried by blood flow through the right chambers of the heart (Swan-Ganz technique) and the position of the catheter identified from the pressure wave form. (b) Pressures in aorta and LV are measured by passing a catheter against the blood flow through femoral or brachial artery. (c) Pulmonary capillary wedge (PCW) pressure – If an end hole catheter passed through a vein is wedged into a small pulmonary artery, or if a balloon catheter is 'floated' as far as possible, and the balloon inflated, the PA pressure will no longer be recorded and the pressure measured will be that of the pulmonary vein and left atrium. This is the 'indirect left atrial' or 'pulmonary wedge pressure'.

Table 7: Normal range of pressure within heart and great vessels

Location	*Pressure (mm Hg)*
Right atrium	
'a'	7
'v'	5
Mean	6
Right ventricle	30/5
Pulmonary capillary	30/15
wedge	
'a'	7
'v'	14
Mean	12
Left ventricle	150/12
Aorta	150/90

Complications

- Damage to arteries and veins with possible thromboembolism.
- Production of arrhythmia.
- Introduction of infection.

Coronary Angiography (CAG)

Coronary angiography is visualization by X-ray of contrast material injected into arteries, veins or heart chambers to define anatomy, disease or direction of blood flow. Basically, there are 3 types of angiography currently available – (1) Conventional film-screen angiography. (2) Intravenous digital subtraction angiography. (3) Intra-arterial digital subtraction angiography.

Coronary cine-angiography – is performed by arterial catheterization under local anaesthesia, usually by percutaneous puncture of femoral or radial artery. A catheter is introduced and guided under radiological control to the left ventricle and left and right coronary arteries in turn. Contrast medium is injected while video and cine images of the recordings are made.

Percutaneous Coronary Angioscopy

Conventional angiography though able to diagnose presence of intra-coronary stenosis, cannot provide information regarding the lesion morphology and intraluminal pathology. PCA provides an accurate three-dimensional view of coronary artery lumen. The chief utility of angioscopy has been in assessing the results of coronary interventions like balloon angioplasty, atherectomies and stenting. The limitations of this procedure are that it cannot see forward beyond tight stenosis or total occlusions and can only gauge surface morphology, being blind to subsurface pathology and plaque composition.

DIGITAL SUBTRACTION ANGIOGRAPHY (DSA)

DSA is a form of angiography where with the help of a computer, a clear image of the blood vessel (without bone overlap) can be obtained.

Table 8: Indications for DSA in cardiovascular cases

• To screen young hypertensives for renovascular cause.
• Occlusive disease of aorta and peripheral vessels.
• Pulsatile masses to rule out aneurysm.
• In the paediatric age group as safe alternative to angiography.
• Post-operative evaluation, e.g. graft patency.
• Follow-up after angioplasty.

IV DSA

Principle – The image acquisition system in DSA consists of a specially designed X-ray image intensifier and television video chain coupled to an image processor, where images are recorded, manipulated and displayed on a cathode ray tube. Images are converted into a digital format. Images obtained before the appearance of contrast material are subtracted from the images obtained after arrival of contrast material in the vessels, so that the resultant image is that of an isolated contrast contained arterial structure. The image is then electrically contrast enhanced to display the final image to its best advantage.

Technique – An antecubital vein is punctured with an 18 gauge needle. A guide wire is then threaded into SVC through the needle. The needle is withdrawn and a 5F high flow digital catheter is introduced over the guide wire and placed into the right atrium. The patient is asked not to breathe for 20–30 seconds during acquisition of the images. The transit time for the contrast material to reach the arterial vessel in question ranges from 4 to 30 seconds. Total dose of contrast material is 150–200 mL.

Indications for DSA in cardiovascular cases (see Table 8).

Advantages

- Simple and safe method and out-patient procedure.
- Avoids arterial puncture complications.

Limitations

1. Patient should be co-operative and have reasonable cardiac output.
2. Less spatial resolution.
3. Not suitable for patients with renal failure because of high volume of contrast.

2. PULSE

IMPORTANCE OF CLINICAL EXAMINATION

1. **Rate:** No absolute normal. Varies in different individuals and in same individual under different circumstances.

Table 9: Abnormalities of rate and rhythm of pulse

Causes of bradycardia
Regular rhythm
1. Sinus bradycardia
2. Complete heart block
3. Partial A-V block with fixed ratio of 2:1 or more
4. S-A block with ratio of 2:1 or more
5. Junctional rhythm (Nodal rhythm)
Irregular rhythm
1. Sinus bradycardia with sinus arrhythmia
2. Partial heart block with irregularly dropped beats
3. S-A block with irregularly dropped beats
4. Atrial fibrillation
5. A-V dissociation (slow type)
Causes of tachycardia
Regular rhythm
• Sinus tachycardia
• Paroxysmal tachycardia
• Atrial flutter
Irregular rhythm
• Atrial fibrillation
• Sinus tachycardia with ectopic beats
• Atrial flutter with varying block
• Paroxysmal atrial tachycardia with block
Causes of irregular rhythm with normal heart rate:
• Multiple ectopics
• Slow atrial fibrillation
• Sinus arrhythmia

In the adult male at rest during waking stage, rate varies between 60 and 80 per minute and in adult female from 70 to 90 per minute. The pulse is slower during sleep. *Bradycardia* is pulse rate less than 60 per minute. *Tachycardia* is pulse rate more than 100 per minute.

Pulse apex deficit – The pulse rate corresponds to heart rate except in the presence of premature contractions or atrial fibrillation, where some of the beats are not transmitted to the radial pulse so that the heart rate exceeds the pulse rate.

2. **Rhythm** – Normal pulse is regular in rhythm. For bedside diagnosis it is important to observe whether the rhythm is regular or irregular and whether the rate is unusually rapid or slow or normal (Table 9).
3. **Volume** – Corresponds to amplitude of the movement or lift of the vessel wall during the passage of the

Table 10: Causes of abnormal pulse volume

Pulse of large volume: In *high cardiac output states*—
Physiological:
• After exercise
• Pregnancy
• Warm humid environment.
Pathological:
• Anaemia
• Fever
• Thyrotoxicosis
• Cor pulmonale
• Cirrhosis of liver
• Systemic A-V fistula
• Systemic hypertension
• Beriberi heart disease
• Paget's disease
• Obesity
• Polycythaemia vera
• Idiopathic hyperkinetic heart syndrome
• Kidney disease: Acute nephritis, or chronic kidney insufficiency
• Carcinoid syndrome
• Polyostotic fibrous dysplasia.
Pulse of small volume (Hypokinetic or weak pulse):
Decreased cardiac output
• CHF, acute myocardial infarction, states of shock, cardiac tamponade, constrictive pericarditis, myocarditis, cardiomyopathy.
Peripheral vasoconstriction
• Shock, hypovolaemia.
Mechanical obstruction
• Mitral stenosis, aortic stenosis, HOCM, coarctation of aorta.

pulse wave. The volume depends on cardiac output (Table 10).

4. **Force –** Corresponds to systolic blood pressure. Press the radial artery against the underlying bone with the more proximal of the two palpating fingers till the pulse wave is no longer felt with the distal finger. More the pressure required to obliterate the pulse higher the systolic blood pressure.
5. **Rate of rise or ascent of pulse** – Normal rate of rise of pulse signifies absence of significant obstruction of outflow at aortic valve. (i) *Rapidly rising pulse*–Light application of examining finger elicits a sharp tap or slap. Very rapid rate of rise with large pulse volume in aortic regurgitation, PDA, thyrotoxicosis. (ii) *Slowly rising pulse* – in aortic stenosis.

Table 11: Causes of unilateral or bilateral weakness of radial pulse

• Ectopic origin and aberrant course of the left subclavian artery
• Proximal compression
– Aneurysm of aorta
– Mediastinal growth
– Cervical rib
– Scalenus anterior syndrome
• Pulseless disease
• Peripheral embolism
• Coarctation of aorta
• In elderly
– Dissection of the aorta
– Aortitis
– Trauma (including iatrogenic)
– Embolism
– Arteriosclerotic obstruction

6. **Tension** – Gives an idea of the diastolic pressure. When the tension is low, the artery is easily flattened and resumes its cylindrical shape without undue resistance. The pulse of low tension appears to collapse between the beats so that nothing is felt at this time. If the diastolic pressure is high, the artery is palpable both in systole and diastole.
7. **Condition of arterial walls** – In arteriosclerosis, the vessel is palpable and can be rolled between the fingers. The inelasticity of a rigid artery may cause a strong pulse to appear weak.
8. **Inequality of pulse** – It is essential to feel one of the larger pulses, such as the carotid or brachial, and the main peripheral pulses should also be felt for. Coarctation of aorta can give rise to discrepant pulses, and an absent or diminished left brachial pulse indicates that the obstruction is at or proximal to the left subclavian artery. Weakness of pulse at the wrist on one or other side may be due to various causes listed in Table 11.
9. **Radio-femoral lag** – In coarctation of aorta, the femoral pulse is delayed when compared to the radial and not synchronous as in normal subjects.
10. **Character or quality of pulse**
    - ***Small weak pulse*** – Often found in conditions with low stroke volume of left ventricle, narrow pulse pressure and increased peripheral resistance, e.g. left ventricular failure, diffuse myocardial disease, constrictive pericarditis, stenosis of mitral, pulmonary or tricuspid valve. A small, weak pulse at rapid rate (thready pulse) in states of shock.

Table 12: Causes of bounding or water-hammer pulse

- *Aortic run off into heart* – Aortic regurgitation, rupture of sinus of Valsalva into a cardiac chamber.
- *Aortic run off into pulmonary arteries* – PDA, aortopulmonary window.
- *Aortic run off into peripheral vessels*
- *Physiological* – Hot bath, alcohol, pregnancy.
- *High output states* – Anaemia, thyrotoxicosis, beriberi, anoxic cor pulmonale, liver cirrhosis.
- *Arteriovenous fistulae* – Vascular malformations, trauma, Paget's disease.
- *Extreme bradycardia* – A-V block.

– ***Large bounding pulse (collapsing pulse)*** – suggests a high pressure associated with an increased flow and is seen in hyperkinetic circulatory states. A very large, bounding pulse of the *water hammer or collapsing* variety is usually associated with an increased stroke volume of LV, a wide pulse pressure and a decrease in peripheral resistance. The pulse strikes the palpating finger with a rapid forceful jerk and quickly disappears. It is described as having a *water hammer quality* because of its sudden impact and a collapsing quality because it falls away so rapidly. The effect is accentuated if the pulse is examined with the patient's arm elevated because the radial artery is then in more direct line with the outflow stream from the aorta.

The collapsing pulse is caused by the artery suddenly emptying as some of the blood flows back from the aorta into the ventricle and may occur in any condition with a large pulse pressure and low diastolic pressure. It indicates a low filling resistance in the reservoir into which the left ventricle pumps its contents. Causes are listed in Table 12.

Twice beating pulse

Dicrotic pulse – The double beat is produced during diastole by an accentuated, palpable dicrotic wave and is likely to be present when peripheral resistance and diastolic pressure are low as in fevers. Aortic regurgitation, mild or moderate dilated cardiomyopathy, severe dehydration, LVF, cardiac tamponade, advanced CHF.

Anacrotic pulse – Rarely the anacrotic notch in severe aortic stenosis may be so marked that it is possible to feel the initial portion of the pulse wave and the main wave as separate waves. This is usually felt in the carotid artery. It may also occur in low output states.

Pulsus bisferiens – The first systolic peak of the pulse (percussion wave P) is followed by second late positive pulse wave (tidal wave T). Found in presence of:

- Combination of moderate AS and severe AR (If P > T, then AR more than AS, if T > P, AS more than AR).
- Severe hypertrophic obstructive cardiomyopathy.

Pulsus parvus et tardus – Small volume pulse (parvus) that rises slowly (tardus) to a late systolic peak due to mechanical obstruction to LV ejection in moderate to severe valvular aortic stenosis. It may be possible to palpate an anacrotic notch on the upstroke of the (carotid) pulse.

Pulsus alternans – A strong and weak beat occur alternately. It results probably from alternate rather than regular contraction of the muscle fibres of the left ventricle, those which respond to one stimulus failing to respond to the next. It may be found in association with left ventricular failure or toxic myocarditis and is a sign of ill omen. In apparently normal persons, pulsus alternans may occur during paroxysmal tachycardia or for several beats following a premature beat.

Jerky pulse – refers to a combination of a small volume pulse and collapsing pulse and is due to the rapid but short-lived ejection from the left ventricle. It is characteristic of hypertrophic cardiomyopathy, but it can also be found in severe mitral regurgitation (particularly when this develops rapidly), and in aortic regurgitation complicated by severe heart failure.

Pulsus bigeminus (coupling) – Recurrent grouping of the heart beats in pairs followed by a pause. *Causes:*

- Ectopic beats.
- Atrioventricular block, every third sinus impulse being blocked.
- Sinoatrial block with ventricular escape.
- Block in atrial flutter alternating between 2:1, 3:1 or 4:1.

Pulsus paradoxus – In normal persons the systolic blood pressure may decline 3–10 mm Hg during inspiration, so that pulsus paradoxus is exaggeration of a normal phenomenon. Although inspiration increases venous return to the right side of the heart, there is relative pooling of blood in pulmonary vasculature as a result of lung expansion and more negative intrathoracic pressure during the active phase of respiration. The net result is a decrease in return of blood to LA and LV and subsequent fall in LV output and decrease in arterial pressure. When the systolic blood pressure falls *more than 10 mm Hg* the pulse is referred to as pulsus paradoxus. The paradox in the pulse is that heart sounds are still audible at a time when no radial pulse is felt.

Causes

- *Limitation of inspiratory increase in blood flow to RV* and pulmonary artery, e.g. superior vena cava obstruction.
- *Greater than normal amount of inspiratory pooling of blood in pulmonary vasculature* causes the intrathoracic pressure to have wide excursions of pressure during inspiration, e.g. asthma, emphysema and airway obstruction.
- *Interference with venous return to either atrium during inspiration,* e.g. pericardial effusion, constrictive pericarditis and patients with severe congestive cardiac failure with markedly raised venous pressure.
- ***Reverse pulsus paradoxus*** indicates inspiratory rise in arterial BP seen in hypertrophic cardiomyopathy, intermittent positive pressure ventilation and AV dissociation.

3. CARDIAC ARRHYTHMIAS

Table 13 gives classification of arrhtythmias according to the site of origin.

Table 13: Classification of arrhythmias according to the site of origin

Sino-atrial node
• Sinus bradycardia
• Sinus tachycardia
• Sinus arrhythmia
• Sinus arrest or block
• Wandering pacemaker
• Sinus extrasystoles
Atria
• Premature atrial contractions
• Atrial tachycardia
• Atrial flutter and fibrillation
• Chaotic atrial rhythm (multifocal atrial tachycardia)
• Atrial standstill
Atrioventricular junction
• A-V junctional premature beats
• A-V junctional tachycardia
• A-V junctional rhythm
• Heart block
Ventricles
• Ventricular premature contractions
• Ventricular tachycardia
• Bundle branch block
• Ventricular flutter and fibrillation
• Ventricular standstill

MECHANISMS

1. *Automaticity* – An abnormal pacemaker overrides the normal pacemaker function at the SA node.
2. *Re-entry* – Re-entry arrhythmias are circular movements of electrical depolarization within cardiac tissue. Re-entry requires the presence of two electrophysiologically different pathways around an insulated core (e.g. the AV valve annulus)
3. *Trigger activity* – is dependent on previous action potential when oscillations in the membrane depolarize the cell to threshold.

ANTI-ARRHYTHMIC DRUGS

Table 14 gives classification of anti-arrhythmic drugs and their actions.

DISTURBANCES OF IMPULSE FORMATION AND CONDUCTION

Sinus bradycardia: Sinus rhythm slower than 60 beats per minute (Table 15) (Fig. 6).

Sinus tachycardia: Sinus rhythm faster than 100 beats per minute (Table 16) (Fig. 7).

Sinus arrhythmia

Respiratory form – The heart rate increases on inspiration and slows at the height of inspiration and during expiration (Fig. 8). Phasic variation more than 10%. When the breath is held the arrhythmia disappears. It is a normal phenomenon and depends on the respiratory variations in vagal tone inhibiting the SA node. This *phasic* type of sinus arrhythmia is common in children and athletes and is also seen in some old people. This variation in pulse rate is absent in patients with ASD.

Non-respiratory form – Phasic variation not related to respiration may occur with vagal stimulation of GI tract or digitalis toxicity.

Ventriculosinus arrhythmia – P-P intervals without intervening QRS complex longer than P-QRS-P intervals. May occur in CHB.

Sinoatrial block (Bradycardia-Tachycardia syndrome): Disorders of sinoatrial conduction and bradycardia-tachycardia syndrome are clearly linked due to the common substrate of conduction delay being the integral part of re-entry mechanisms.

Manifestations: Of sinus node dysfunction (sick sinus syndrome).

1. Persistent, severe and unexpected sinus bradycardia.
2. Sinus arrest with an escape or junctional rhythm. Sinus arrest is momentary failure of SA node to initiate an impulse.

Table 14: Classification of anti-arrhythmic drugs and their actions

Drug	*Dosage*	*Indications*	*Toxic effects*
Class I: *Sodium block*			
IA: Membrane stabilising agents			
Quinidine	200–400 mg q6h	Vent. arrhy. VPCs, VT	GI disturbances Cinchonism Widening of QRS
Procainamide	PO 250–1000 mg q3h IV 20 mg/min for 30-40 min	Junct. arrhy. Ectopics, tachy.	GI disturbances Hypotension after IV Lupus syndrome
Disopyramide	100–200 mg q6-8h	Supravent arrhy. APCs, PAT, AF, A flutter	Xerostomia Urinary retention Hypotension QRS prolonged
IB: Effect on vent. refractoriness			
Lidocaine	Bolus 75 mg, then 50 mg q5 min to total 225 mg	Ventricular arrhythmias	CNS: Lightheadedness, confusion, dizziness, tinnitus CVS: Bradycardia, hypotension
Mexiletine	200–400 mg q8h	Ventricular arrhythmias	GI: Nausea, vomiting CNS: Dizziness, lightheadedness, tremor
Phenytoin	250 mg in normal saline over 10 min, then 100 mg q5 min as needed	Digoxin toxicity arrhythmias	Nystagmus, ataxia, slurred speech, confusion, dizziness
IC: Effect on repolarization			
Flecainide	100–200 mg q12h	Sustained VT Symptomatic non-sustained VT Vent. ectopy	Prolonged PR, QRS. BBB Sinus node dysfunction Dizziness, visual disturbance Proarrhythmia
Encainide	20–50 mg q8h	Vent. arrhythmia	VT, V. Fib. Dizziness, blurred vision Rash. Proarrhythmia
Propafenone	150 mg q8h	Vent. arrhythmia Atrial arrhythmia (including WPW syn.)	Proarrhythmias Bronchospasm Dizziness
Class II: *Beta-blockers*			
Propranolol	PO: 20–80 mg q6h IV: 1-3 mg in NS (0.5–1 mg/min.)	SVTs PVCs AF and A flutter (Reduce vent. response)	Bradycardia Bronchospasm Heart failure Hypotension
Esmolol	Bolus 500 µg/kg, then 50 µg/kg/min for 4 min.	PVCs AF and A flutter (Reduce vent. response)	
Metoprolol	PO: 25-50 mg q12h	PVCs	
Class III: *Prolongation of action potential and repolarization*			
Sotalol	40 mg q6h	PVCs VT	Impaired peripheral circulation, bradycardia, hypotension
Amiodarone	PO: 800–1600 mg q6h Maint. 200–600 mg q6h IV: infusion with loading dose of 5 mg/kg over 20 mins, followed by infusion of 1 g/24 h for 48–72 h	PVCs VT, VF	Corneal microdeposits Thyroid abnormalities Photosensitivity Pul. fibrosis Bradycardia Proarrhythmia
Bretylium	Bolus 5–10 mg/kg, then 1–2 mg/kg/min or repetitive bolus of 5–10 mg q6h	VT VF	Hypotension Increased arrhythmia
Class IVA: *Calcium-channel blocking agents*			

Contd...

Contd...

Drug	*Dosage*	*Indications*	*Toxic effects*
Verapamil	PO: 80 mg q6–8h IV: 5–10 mg over 2–3 min. Repeated after 15–30 min. if necessary	SVT	Occasional hypotensive symptoms, headache
Diltiazem	PO: 30–60 mg q6–8h IV: 0.05–0.45 mg/kg over 2 min.		Minimal
IVB K+ channel openers			
Adenosine	IV 0.05 mg/kg as bolus with 0.05 mg/kg increments at 2 mins intervals up to 0.25 mg/kg	Junctional tachycardias	Few side effects Transient marked slowing (sinus bradycardia or complete AV block)
Other drugs: *Digitalis*			
Digoxin	Loading: 1.25 mg over 24 h Maint. 0.25 mg/day	AF, Atrial flutter AT	GI: Anorexia, nausea, vomiting Blurred vision or chromatopsia Gynaecomastia Rhythm disturbances

Table 15: Causes of sinus bradycardia

Non-cardiac
• Athletes
• Normal during sleep and in elderly
• After viral infections
• Increased vagal tone (simple syncope)
• Increased intracranial pressure
• Drugs: Beta blockers, calcium antagonists, amiodarone, clonidine
• Hypothyroidism
• Hypothermia
• Cervical or mediastinal tumours
• Gram-ve sepsis
• Obstructive jaundice
Cardiac
• 2nd and 3rd degree heart block

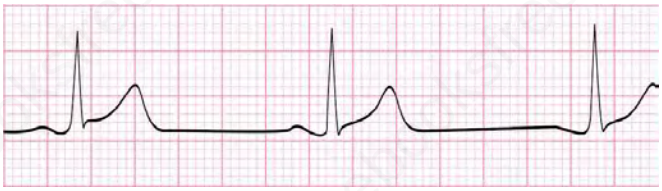


Fig. 6: Sinus bradycardia. Rate 50 per minute

Table 16: Causes of sinus tachycardia

Non-cardiac
• Infancy and childhood
• Emotional stress
• Anaemia or haemorrhage
• Fever
• Pregnancy
• Hypovolaemia
• Shock
• Drugs: Sympathomimetics, atropine group
• Alcoholism
• Carcinomatosis
Cardiac
• Myocardial ischaemia or infarction
• Myocarditis
• Untreated heart failure

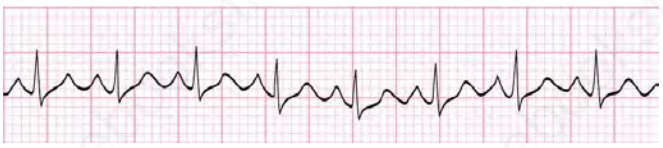


Fig. 7: Sinus tachycardia. Rate 120 per minute

Causes – Acute MI, myocarditis, digitalis, type Ia antiarrhythmic drugs, fibrotic changes in SA node and atria.

When the SA node fails to initiate an impulse, one of the following may occur:

a. SA node resumes – SA node takes over and a normal rhythm is restored. The P-P interval during the

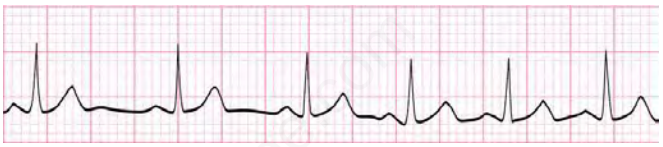


Fig. 8: Sinus arrhythmia. P-P interval shortens with inspiration and lengthens with expiration

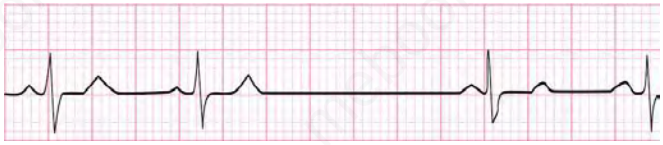


Fig. 9: Sinus arrest. A pause during which a PQRST complex is dropped

block is not an exact multiple of the normal P-P interval (Fig. 9).

b. Escape beat – An ectopic focus in the atria, node or ventricle may take over or 'escape' from their usual control by a higher pacemaker in order to maintain the heartbeat. If the ventricular escape continues for two or more beats, it is designated idioventricular rhythm. *Treatment* – Permanent pacemaker if symptoms such as syncope.

3. Prolonged sinus arrest with failure of all subsidiary pacemakers resulting in total cardiac asystole.
4. Chronic atrial fibrillation with an unusually slow ventricular response not due to drug therapy.
5. Inability of the heart to resume sinus rhythm following electrocardioversion for atrial fibrillation or flutter.
6. Alternating bradyarrhythmias with tachyarrhythmias – Here sinus bradycardia (with or without sinus pauses) is associated with episodes of tachycardia. Occasionally, the sinus node may be very slow to restart after a paroxysm of tachycardia and there may be a period of sinus arrest. Drugs used to prevent tachycardia accentuate bradycardia and sinus pauses and may worsen the condition. Since these medications (beta-blockers, calcium antagonists) are used to treat the tachyarrhythmias, concomitant permanent pacing may be required.
7. Silent atrium – Occasionally, the atria fail to depolarise or to contract. P waves are absent from the ECG and cardiac rhythm is maintained by a lower centre, usually a junctional focus.

PREMATURE CONTRACTIONS (ECTOPIC BEATS)

Cardiac contractions which arise prematurely from a normal or abnormal pacemaker.

1. ***Premature Atrial Contractions (PACs)***

   Causes – Rheumatic heart disease notably mitral valve disease, congenital or acquired non-rheumatic MR, ischaemic heart disease, thyrotoxicosis, acute or chronic lung disease, ASD, thoracic surgery, alcohol, tobacco or caffeine excess, idiopathic.

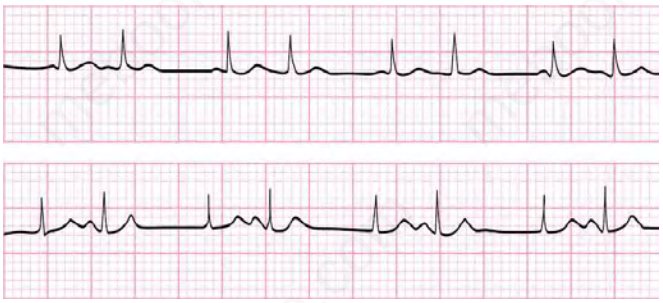


Fig. 10: Atrial premature beats producing atrial bigeminy

ECG – Abnormal P wave configuration which is usually followed by a normal QRS (Fig. 10). The P-wave which may be hidden within the preceding T wave is usually upright but may be inverted or biphasic. PR interval more than 0.12 sec. No QRST complex following P wave if impulse reaches AV node when it is refractory (blocked atrial ectopic).

Clinical significance – (i) If associated with underlying heart disease they may herald other atrial arrhythmias. (ii) Occurring in mitral stenosis they presage onset of atrial fibrillation. (iii) Multifocal extrasystoles do not occur with a normal heart.

2. ***Junctional (Nodal)***

   Causes and significance –same as PACs.

   ECG – Premature P wave followed by QRST complex or P wave buried in QRS complex or follows it. Full compensatory pause. PR interval less than 0.12 sec. (Fig. 11).

3. ***Premature Ventricular Contractions (PVCs)***

   Causes

   - Idiopathic
   - Organic heart disease – Ischaemic heart disease, hypertensive heart disease, myocarditis, any cause of ventricular hypertrophy such as cardiomyopathy, mitral valve prolapse.
   - Drugs – Digitalis, quinidine, amphetamine, caffeine, thyroxine, adrenaline, nicotine.
   - General – After major illness, or surgery, physical unfitness.

   Grading of ventricular ectopy:

   1. <30 uniform VPCs hour.
      A. <1/min.
      B. >1/min.
   2. >30 uniform VPCs/hour
   3. Multiform VPCs
   4. A. Bigeminy

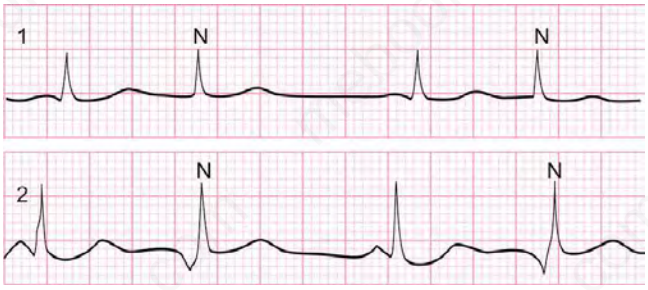


Fig. 11: Nodal ectopic beat. There is no P wave before the premature beat

B. Trigeminy

5. R-on-T phenomenon

ECG–QRS wide, and notched or slurred. T wave in opposite direction to QRS. P wave hidden in or follows QRS. Shape varies if multifocal. Fully compensatory (Fig. 12).

Clinical significance – (1) Idiopathic and may occur in health. May be caused by emotional upset, may occur during pregnancy. (2) Effect of exercise – (a) If abolished by exercise tachycardia they are usually considered benign. (b) If induced by exercise they may suggest presence of coronary insufficiency. (3) In acute MI, PVCs are a warning for more serious arrhythmias. In LBBB, PVCs may be the only ECG evidence of cardiac infarction. (4) A special subgroup of patients with mitral valve prolapse are at higher risk for serious ventricular arrhythmias. (5) Grading of ectopics – Complex and frequent ectopy is associated with increased risk of sudden death, while low grade ectopy has a benign prognosis.

4. *Interpolated extrasystole* – Occurrence of three beats in rapid succession in the time normally occupied by two and without a long pause. Common with ventricular ectopic beats.
5. *Fusion beats* – QRS complex intermediate in shape between a normal and aberrant QRS and preceded by a P wave.

Symptoms

1. No symptoms in about 50%.
2. Disagreeable sensation due to large beat or fear of heart stopping due to long pause.
3. Pain and neurosis in hypersensitive subjects.
4. Dizziness and faintness if premature beats numerous.

Signs

- *Pulse* – Quick beat followed by pause, less than compensatory in atrial and nodal and equivalent to two sinus cycles in ventricular premature beat ending in pulse more forceful than its predecessors. Early beat faintly palpable or impalpable at peripheral pulse (pulse deficit).
- *Heart sounds* – (a) 1st sound – Generally accentuated in all ectopic beats since filling of the ventricles is interrupted and valves are still open. (b) 2nd sound– Normal splitting in atrial and nodal and wide splitting due to ventricular asynchrony. If ectopic beat is so premature that there is insufficient ejection of blood, no 2nd sound.
- *Cannon waves* – In ventricular premature beat, cannon 'a' wave in jugular pulse coincides with or just follows 1st heart sound or carotid impulse in contrast with cannon wave in atrial premature beat which just precedes 1st sound or carotid impulse.

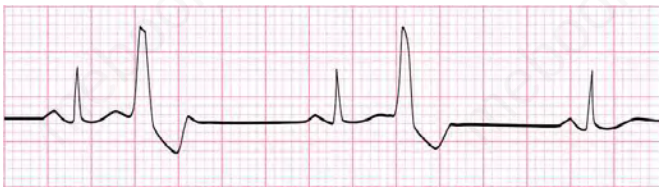


Fig. 12: Ventricular ectopic beats causing coupling or bigeminy

Treatment

1. *If no underlying organic heart disease* – (a) Reassurance regarding harmlessness of the condition. (b) Sedatives. (c) If persistent – Low-dose beta blocker.
2. *Removal of causative or aggravating factors* – Excessive intake of tea, coffee, alcohol, tobacco. Stress.
3. *Acute suppression* – e.g. acute MI (Refer). Digoxin fab for digitalis toxicity. Prophylactic IV lidocaine or procainamide may be used during thrombolysis or PTCA.
4. *Chronic cardiac disease* – Use of class Ia agents. Amiodarone if sustained arrhythmia that fails to respond to conventional agents.

NARROW COMPLEX TACHYCARDIAS

ATRIAL FIBRILLATION

Causes of atrial fibrillation are listed in Table 17.

Clinical Classification

1. **Paroxysmal AF:**
   (a) Transient AF lasting less than 48 hours
   (b) Persistent: Episode of AF lasting more than 48 hrs 7 days.
2. **Permanent AF:** Sinus rhythm cannot be restored by pharmacological and non-pharmacological methods

Table 17: Causes of atrial fibrillation

I.	***Paroxysmal and unrelated to underlying heart or other organ disease including 'lone' AF.***
II.	***Cardiac***
	A. Valvular heart disease
	• Mitral stenosis
	• Mitral annular calcification
	• Mitral valve prolapse
	B. Nonvalvular heart disease
	• Ischaemic heart disease – Acute MI, Prinzmetal's angina, thrombolysis in acute MI, balloon deflation during PTCA.
	• Hypertensive heart disease.
	• Myocarditis
	• Cardiomyopathy particularly dilated and hypertrophic.
	• Pericarditis – Viral, postcardiotomy, postinfarction.
	• Atrial septal defect.
	• Post-operative – especially after thoracotomy or coronary artery bypass.
	• Pulmonary thromboembolism
	• Sick sinus syndrome
	• WPW syndrome
	• Atrial myxoma
III.	***Systemic disorders***
	• Hypoxia due to lung disease.
	• Infection acute (e.g. pneumonia) or chronic
	• Hyperthyroidism.
	• Cerebral vascular accident.
	• Electrolyte imbalance.
	• Hypotension and shock.
	• Drugs: Theophylline, amphetamines, adrenaline.
	• Alcohol, caffeine.

Lone AF occurs more in males and is resistant both to drugs and electroversion.

Mechanisms

1. Re-entry is the primary mechanism
2. Multiple wavelets hypothesis – Grossly irregular wave fronts become fractionated into daughter wavelets, the more the wavelets, more likely for the arrhythmia to sustain.

Symptoms

- *Few or no symptoms* – If no underlying heart disease, or slow fibrillation.
- *Due to rapid heart rate* – Palpitation or thumping in chest.
- *Due to fall in cardiac output and systemic pressure* – (a) Anginal pain because of lowered coronary perfusion if coronary insufficiency. (b) Weakness, dyspnoea and cough due to heart failure. (c) Syncope or focal neurological symptoms such as hemiparesis, aphasia, etc. if cerebral artery narrowing.
- *Symptoms due to embolism*–if rheumatic mitral valve disease.

Signs

- *Irregularly irregular rhythm* – With ventricular rate usually between 100-200 beats per minute. Slower ventricular rate in old age, digitalis therapy or lone atrial fibrillation.
- *Pulse apex deficit* – Pulse rate considerably less than apex rate because some systolic contractions are feeble.
- *Heart sounds* – Variation in intensity of 1st sound. 2nd sound may not be heard if the ventricular contraction is too weak to open the semilunar valves.
- *Murmurs* – Systolic murmurs preserved, louder following longer cycles and fainter after shorter cycles. No presystolic accentuation of diastolic rumble of mitral stenosis except when there is a short diastole.
- *Neck vein pulsations* – Rarely rippling fibrillary waves. Usually no evidence of either atrial contraction or relaxation i.e. no 'a' waves or negative x descent.

ECG – (Figs. 13 to 15) (a) Absence of normal P waves. (b) Presence of fibrillary waves. (c) Amplitude of R wave varies from beat to beat.

Differential Diagnosis

See Table 25.

Management

1. Treatment of underlying Heart disease (if any), or the precipitating cause – e.g. control of ischaemic heart disease, antidigoxin antibodies for digitalis toxicity arrhythmia.

Paroxysmal AF

i. **If no associated heart disease** – Rest, sedatives and digitalis for short paroxysms. For recurrent paroxysms control of ventricular rate with digitalis, beta blockers or calcium antagonists.

ii. **If patient haemodynamically stable** – Class Ia antiarrhythmic drugs to convert to sinus rhythm. Quinidine is the most widely used 200–600 mg every 6 to 8 h. Careful monitoring of QT intervals for prolongation of QT interval and also serum drug levels during attempted chemical cardioversion. The class III agents sotalol and dofetilide can be administered to patients

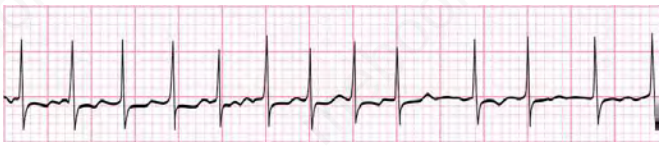


Fig. 13: Atrial fibrillation with rapid rate

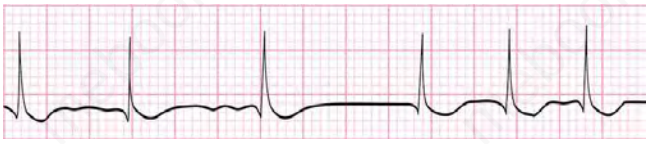


Fig. 14: Slow atrial fibrillation Digitalis effect

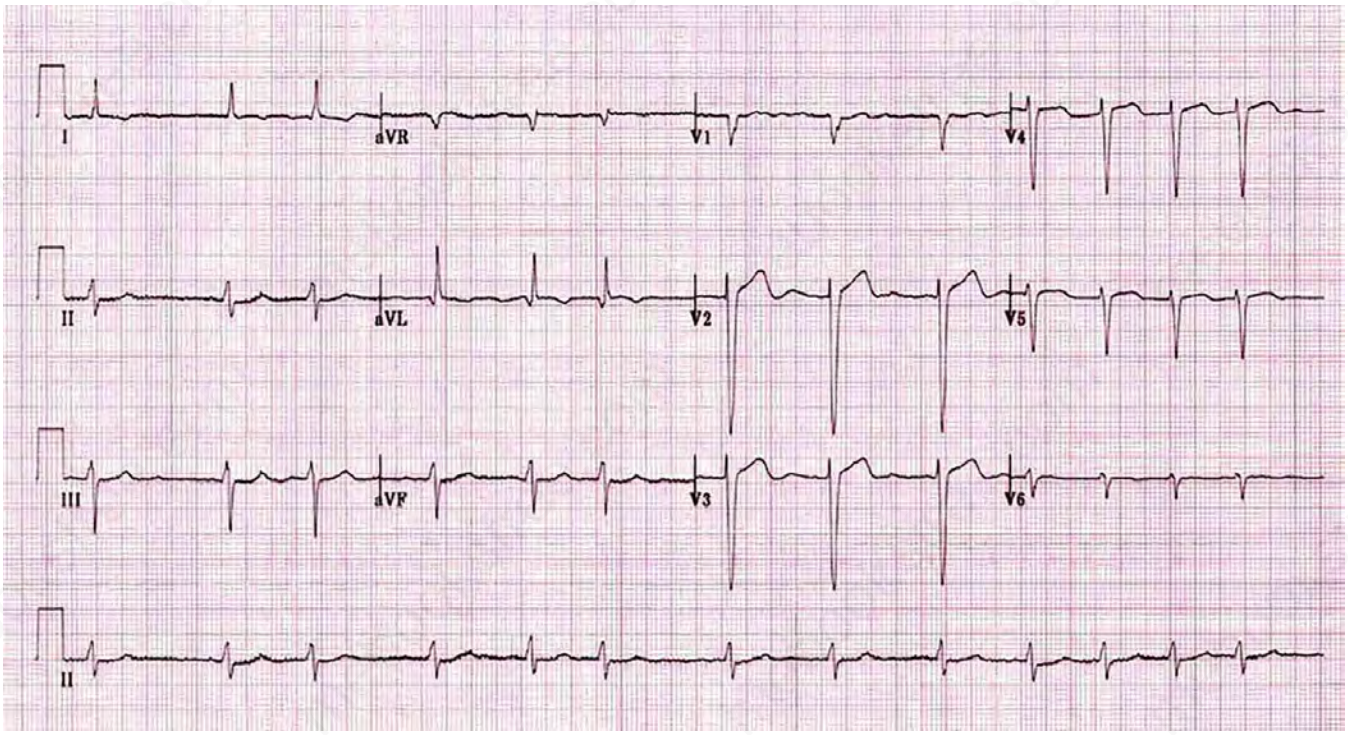


Fig. 15: 12-lead ECG showing atrial fibrillation

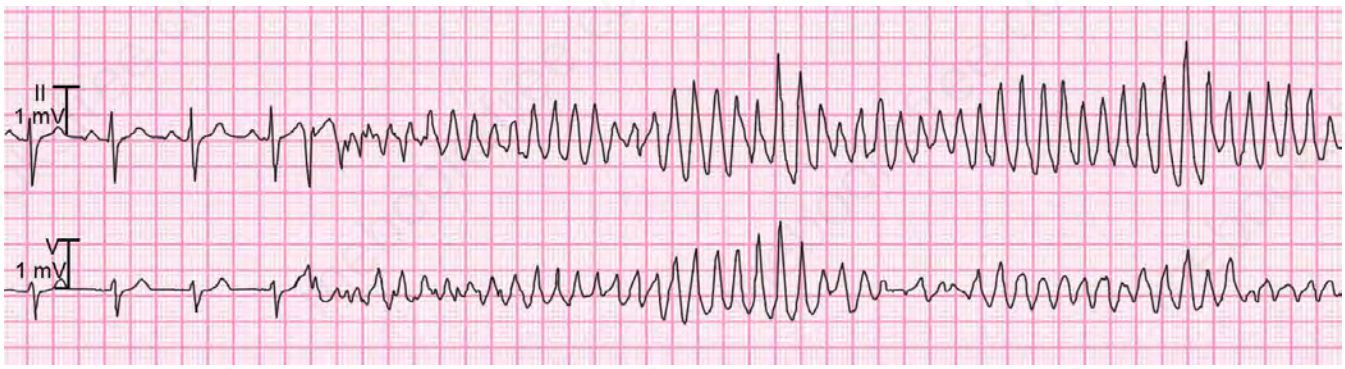


Fig. 16: ECG sharing polymorphic ventricular tachycardia

with coronary artery disease or structural heart disease but have risk of inducing excessive QT prolongation and torsades des pointes (Fig. 16).

iii. **If haemodynamically unstable, significant AS or MS** – DC cardioversion to prevent or reverse pulmonary oedema.

Table 18: Drugs for conversion and maintenance of AF

Drug	*Dosage*	*Comments*
Quinidine		
Recent AF	1.5 g/d po	Proarrhythmia
Chronic AF	200–600 mg q6h po	
Procainamide	1.5 g/d po 10–15 mg/kg iv (loading), 2–4 mg/min iv	No significant side effects
Flecainide	100-200 mg q6h po	Contraindicated in severe LV dysfunction
Amiodarone	5 mg/kg iv over 20–30 mins, followed by infusion 1 g/24h for total 24–48 h 200 mg/d po maintenance	Severe bradycardia with iv dosing

Table 19: Cardioversion in atrial fibrillation

Indications
Recent onset AF
Prior peripheral embolism
Persistent AF after treatment of underlying cause
Rapid ventricular rate despite drugs
Persistent symptoms related to AF after medical treatment
Contraindications
Relative
AF > 1 year
Left atrial size > 50 mm
EF < 25%
Absolute
Digitalis toxicity
Underlying cause sick sinus syndrome

Sustained AF

a. **Patient HD unstable with heart rate 170–200/min.** – DC cardioversion with 50–100 J, increased if necessary to 200J.

b. **Patient HD stable** (and no emergency) – IV digoxin to slow ventricular rate. Dose 0.5 mg slowly over 5 min, then 0.25 mg q4h till ventricular rate < 100/min, or total dose of 1.5 mg is given. Patient may revert to sinus rhythm.

Drugs used for conversion and maintenance of AF are given in Table 18.

Conversion to sinus rhythm – Most of the following criteria should be met:

- AF has been present for < 1 year.
- LA size (echo) is < 45 mm.
- LV function (echo) is normal or nearly normal.
- Age < 75 years.
- No intracardiac thrombi (TOE).

Cardioversion

Indications and contraindications for cardioversion are given in Table 19.

Note: All patients with AF of more than two days duration should be placed on Warfarin for 3 weeks prior to conversion, and 4 weeks following cardioversion, until sinus rhythm has been established.

In AF both atria fibrillate hence right-sided embolization can occur from clot in RA.

Chronic AF

Drugs used to control ventricular rate are listed in Table 20.

Table 20: Control of ventricular rate

Drug	*Loading dose*	*Maintenance dose*
Digoxin	0.75–1 mg IV 0.75–1.5 mg po	0.125–0.25 mg/po
Esmolol	500 µg/kg/min IV	50–300 µg/min IV
Verapamil	5–10 mg IV	80 mg q6h po
Diltiazem	0.25 mg/kg IV	30–90 mg q8h po

Anticoagulation to prevent systemic and pulmonary embolization – *Indications:*

- Rheumatic mitral valve disease with recurrent, persistent or chronic AF.
- Dilated cardiomyopathy with recurrent, persistent or chronic AF.
- Elective cardioversion with mitral valve disease, prosthetic valves, dilated LA or previous events.
- Coronary or hypertensive heart disease and prior embolic episodes related to AF.

Contraindications – Prior bleeding events, uncontrolled hypertension, malignancy.

Catheter Ablation

Radiofrequency AV node ablation for drug resistant AF. The ejection fraction improves. Permanent pacing is required following ablation.

Surgical Treatment

Underlying principle is the hypothesis that critical mass of atrial tissue is required to sustain AF. The 'corridor' (MAZE) operation is designed to maintain sinus rhythm by isolating the sinus node by a small corridor connecting atrial tissue and AV node from remaining atrial tissue.

ATRIAL FLUTTER

Causes

Same as A. fibrillation, more often associated with heart disease than AF.

Diagnosis

1. *Pulse* – (a) Regular rate of about 150 per minute. (b) Abrupt drop in rate to half the previous rate due to shift from 2:1 to 4:1 block may occur.
2. *Jugular venous pulse* – Regular small rapid pulsations (flutter waves) may be seen.
3. *Heart sounds* – 1st heart sound may vary in intensity due to minor changes in P-R interval.
4. *Carotid sinus pressure* – Usually slows the ventricular rate to half. On release of pressure ventricular rate returns to previous level.
5. *ECG* – Saw-tooth (picket fence) appearance of atrial waves (Figs. 17 and 18) with ventricular response following every 2nd, 3rd (up to 8th) P wave.

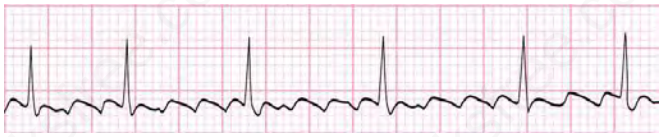


Fig. 17: Atrial flutter with varying block

Differential Diagnosis

See Tables 24 and 25.

Management

Note: Any SVT at rate >150/min should be considered to be due to AFL unless proved otherwise.

Patient HD unstable (Low BP, restlessness, tachycardia, tachypnoea, acidosis) – (a) Cardioversion with 25–50 J or (b) Overdrive pacing of atria at frequency higher than flutter rate.

Patient HD stable: Reduce ventricular rate to 100/min – (a) Heart rate >140/min and no LV dysfunction – Verapamil 5 mg IV, repeat if necessary after 30 min. May convert to sinus rhythm. Danger of marked hypotension (treated with IV calcium).

Atrial flutter with LV dysfunction–IV digoxin 0.25–0.5 mg. Repeat after 2–4 h. Total in 24h 1–1.75 mg. If AF persists and reversion to sinus rhythm is desired: Quinidine 0.4 g q2h for 4–5 doses, then maintenance doses of 0.2 g q6h or Procainamide 500 mg q4h, then reduce to 500 mg q6h.

Note: Quinidine or procainamide should not be given till ventricular rate is slowed by verapamil or digoxin.

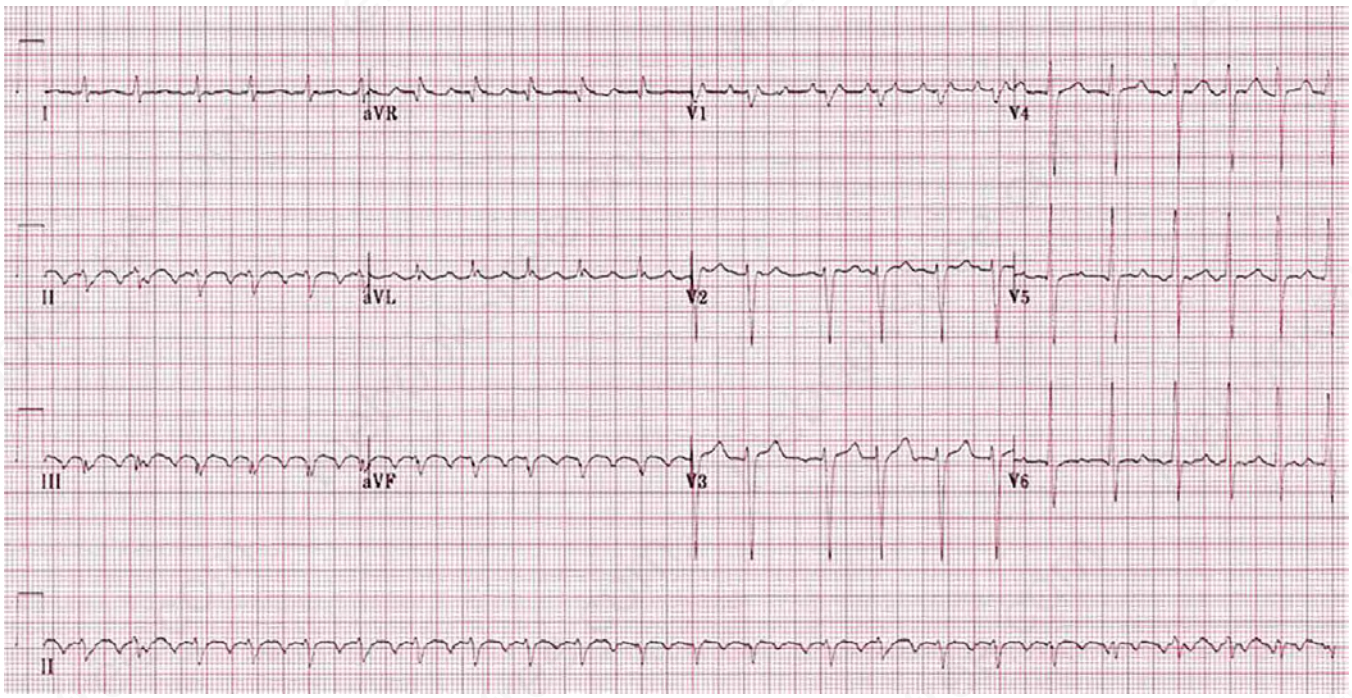


Fig. 18: 12-lead ECG showing atrial flutter with 2:1 block

Atrial pacing – may convert atrial flutter to sinus rhythm. Especially suited to patients who are a poor risk for anaesthesia used in giving DC shock such as elderly patients, those with acute myocardial infarction or advanced obstructive lung disease.

Prevention of Recurrence

Quinidine 200 mg qds. or sustained release tablets in a dose of 800–1200 mg/day, or slow release procainamide 500–750 mg po q6h may be given or added to propranolol with restoration of sinus rhythm. Amiodarone can be tried for refractory cardiac failure. After a 3-week loading period, sinus rhythm may be restored by electrical cardioversion and maintained by amiodarone 200 mg po daily.

PAROXYSMAL TACHYCARDIA

Presence of six or more successive ectopic beats.

Classification

1. Supraventricular:
   Atrial
   A-V junctional (Nodal)
2. Ventricular

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA (PSVT)

Causes

- Idiopathic in majority.
- As for atrial ectopics – notably rheumatic and ischaemic heart disease.
- Digitalis intoxication.
- Pre-excitation (Wolff-Parkinson-White syndrome).
- Short PR interval with normal QRS complex (Lown-Ganong-Levine syndrome).

Symptoms

- *Local* – Precordial discomfort or anginal pain. Disagreeable fluttering over precordium. Fullness in neck. Pounding of vessels in head, arms, abdomen and leg.
- *Psychic and reflex nervous symptoms* – Anxiety, coldness, sweating, and dizziness. Abdominal distension, nausea and vomiting. Polyuria at end of attack.
- *Cardiovascular* – If heart diseased or paroxysm prolonged – (a) Symptoms due to cerebral ischaemia – Syncope or Adams-Stokes syndrome. (b) Cardiac failure especially when there is underlying heart disease or in children.

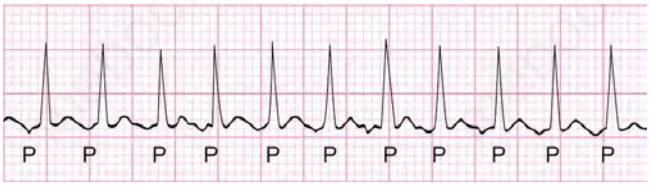


Fig. 19: Paroxysmal atrial tachycardia

Signs

- Regular heart rate of 160–220/min.
- Changing intensity of S_1 in junctional tachycardia and atrial tachycardia with varying block.
- Vagal stimulation by carotid sinus pressure or Valsalva manoeuvre may cause sudden reduction in heart rate.

ECG – Three types of patterns:

- Rapid rate with normal ventricular complexes. Atrial activity is often difficult to identify but there is 1:1 A-V response (Fig. 19).
- A faster atrial rate with 2:1 response found in digitalis toxicity and acute ischaemia.
- 1:1 A-V response with aberrant A-V conduction resembling bundle branch block and simulating ventricular tachycardia.

PSVT DUE TO AV NODAL RE-ENTRY

A benign disorder and the most common form of PSVT. It is characterised by two functionally distinct pathways (slow and fast) within the AV node.

ECG – Retrograde P waves appear buried within QRS or appear immediately after (Figs. 20 and 21).

Differential Diagnosis

See Table 24.

Management

A. **Of attack:**

1. **Sedation and reassurance**
2. **Vagotonic manoeuvres** – (i) Carotid sinus massage, first on right, then on left side for 3 to 5 seconds at a time. Should not be done in patients with history of cerebrovascular insufficiency. (ii) Valsalva manoeuvre – Have the patient inhale deeply, hold his breath and then strain down hard when he counts slowly to 10. (iii) Drinking a glass of ice-cold water. (iv) Induction of gagging or vomiting by placing a finger in the oropharynx. (v) "Diving reflex" – While the breath is held the patient immerses his face into a basin of cold water.

3. **Drugs**

   Drugs used in treatment of PSVT are given in Table 21.

4. **Cardioversion** - (a) If above measures unsuccessful, in presence of hemodynamic instability. (b) If medical therapy ineffective or poorly tolerated or when differentiation from ventricular tachycardia is difficult because of bundle branch block. Digitalis should be discontinued before cardioversion. Relative contraindications to DC shock include digitalis toxicity, hyperkalaemia, anaesthetic risks and frequently recurrent arrhythmia.

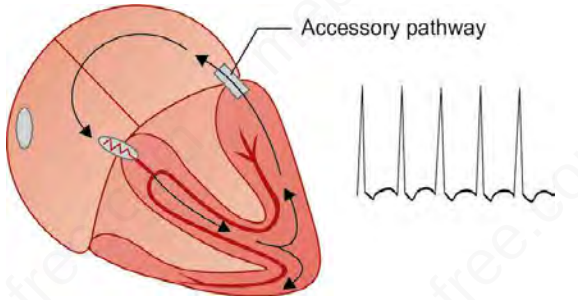


Fig. 20: Atrioventricular nodal re-entry tachycardia (AVNRT)

5. **Ablation of electrical pathway** – (AV node or accessory connections) by catheter or surgery.
6. **Pacing devices** – designed to interrupt paroxysms of tachycardia and restore sinus rhythm.

B. **Prevention of recurrence:**

1. **General measures** – Use of sedatives and avoiding excess fatigue, emotional tension, excess alcohol, smoking, and stopping use of sympathetic drugs if any.

Table 21: Drugs used in treatment of PSVT

Drugs	*Dosage*
Adenosine	6 mg as initial rapid IV bolus. If ineffective within 2 mins, further 12 mg bolus which may be repeated once.
Verapamil	5 mg IV over 5 mins. Can be repeated every 5 minutes until conversion occurs, or total dose reaches 20 mg.
Digoxin	0.5 mg over 10 mins. IV followed by additional 0.25 mg every 4 h to maximum of 1.5 mg in 24 h.
Esmolol	Loading infusion of 500 µg/kg/min. If no response within 5 mins, same dose to be repeated followed by maintenance infusion 500 µg/kg/min.
Diltiazem	0.25 mg/kg as bolus over 2 mins. If response inadequate second dose after 15 mins 0.35 mg/kg.

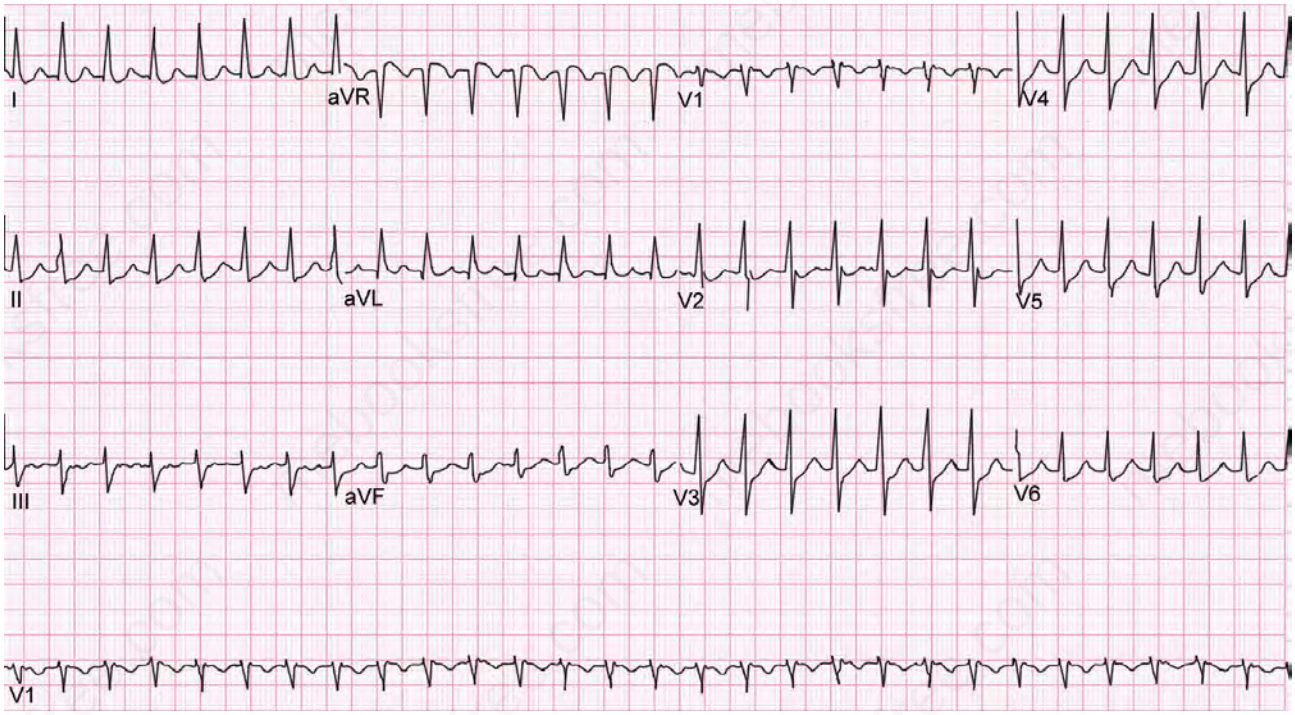


Fig. 21: 12-lead ECG atrioventricular nodal reentrant tachycardia (AVNRT)

2. **Drugs** – Verapamil 80 mg. t.d.s. or Digoxin 0.25 mg. once a day, or Quinidine 0.2 g. qds., or Propranolol 10–40 mg. qds.

II. ***PSVT due to WPW syndrome*** – In sinus rhythm, the presence of the accessory pathway results in pre-excitation of the ventricle which produces the delta wave and short PR interval on the ECG.

ECG – P wave seen in ST segment (Figs. 22 and 23).

W-P-W syndrome: It is associated with Ebstein's anomaly, HCM, and mitral valve prolapse. AF is the main risk of sudden death if conduction is 1:1 down in accessory pathway causing VF.

Treatment – Vagal manoeuvres. Verapamil, propranolol or Class I antiarrhythmic agents. Digoxin contraindicated.

III. ***Ectopic atrial tachycardias*** (Long RP tachycardia) – Characterised by abnormal P-wave vector, low P-wave amplitude and rapid rate (160–240/min). If associated with high-grade AV block (PAT with block) digitalis toxicity is likely.

ECG – P wave falls before QRS complex

Treatment – (a) Of precipitating factor, e.g. decompensated COPD, electrolyte imbalance, metabolic abnormalities, hypoxia, thyrotoxicosis. (b) Antiarrhythmic agents effective if no reversible cause.

Multifocal atrial tachycardia (MAT) usually occurs in patients with severe pulmonary or heart disease in relation to acute respiratory insufficiency. Rate usually <150/min.

ECG – Three or more different configuration ectopic P waves (Fig. 24).

Treatment – of underlying cause. Verapamil or quinidine in maintenance doses.

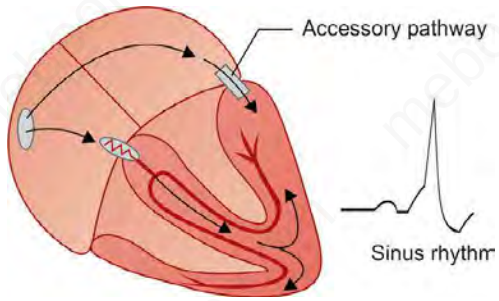


Fig. 22: WPW syndrome

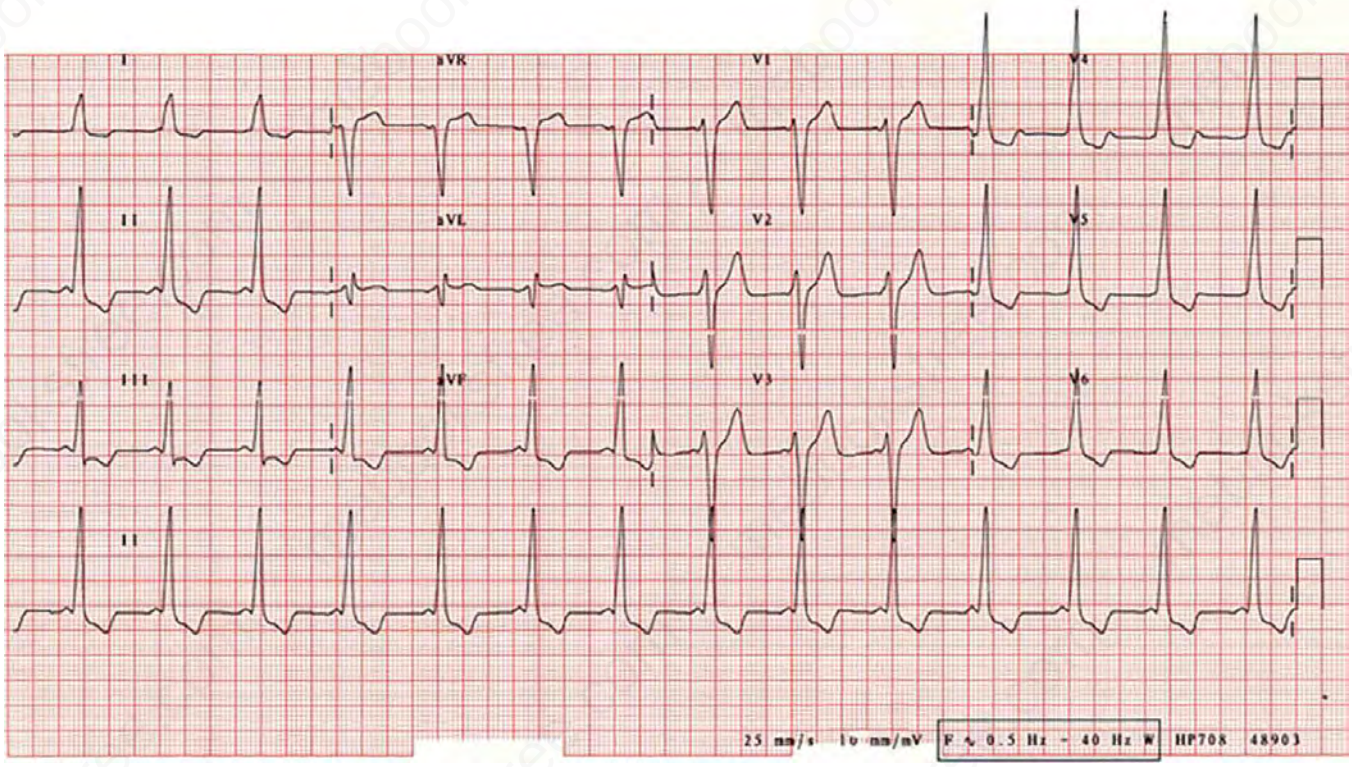


Fig. 23: 12-lead ECG in WPW (pre excitation) syndrome. Note short PR interval and delta waves (slurred initial portion of QRS complexes)

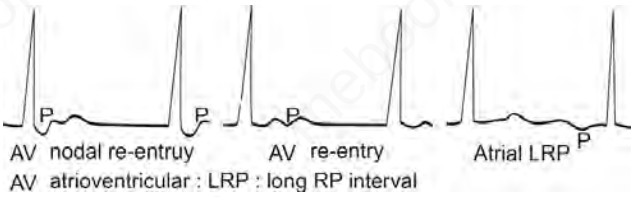


Fig. 24: ECG features of various SVTs

Wandering atrial Pacemaker: Here the rhythm of the heart is not controlled exclusively by the sinus node, but other foci in atrium (and occasionally AV junction) fire and conduct to the ventricles.

ECG – Different P wave configurations and different PR intervals.

Treatment – Permanent pacemaker if patient symptomatic. Later appropriate drugs for control of tachyarrhythmia.

Lown-Ganong-Levine Syndrome: Association of bouts of tachycardia with, between attacks, short PR interval but no delta wave and no prolonged QRS. PT is usually supraventricular but may be ventricular.

Supraventricular tachycardia with aberrant condition

SV conduction of SVT, either atrial or junctional results in broad QRS complexes. This may be caused by either left or right bundle branch block which may be permanent and present in sinus rhythm or may be rate-related and present only during tachycardia. An ECG may be of value with typical BBB pattern seen in SVT and more bizarre morphologies in VT.

BROAD COMPLEX TACHYCARDIA
VENTRICULAR TACHYCARDIA (VT)

A series of 3 or more consecutive ventricular complexes.

Causes

These are listed in Table 22.

Table 22: Causes of ventricular tachycardia

• Ischaemic heart disease
– Chronic or variant angina
– Acute myocardial infarction
Following recovery from infarction particularly those complicated by development of ventricular aneurysm
• Most of the causes of ventricular ectopics.
• Idiopathic paroxysmal or intermittent variety rarely in youth.
• Drug toxicity
– Digitalis
– Quinidine
– Sympathomimetic drugs

Diagnosis

See Table 24 of differential diagnosis of tachycardias.

ECG – Wide and bizarre QRS complexes usually at a rate of 160 or more (Fig. 25). P waves independent of QRS complexes at normal sinus rate but as a rule difficult to detect. The rhythm may be slightly irregular (Table 23). Carotid sinus massage has no effect.

Management

Any wide complex tachycardia should be treated as an emergency as if it is VT.

1. **Non-sustained VT —** No treatment unless associated cardiac disease. Removal of potentially reversible causes if present, e.g. IHD, hypoxaemia, acidosis, electrolyte abnormalities (hyperkalaemia, hypocalcaemia, hypomagnesaemia), hyper-thyroidism, digitalis toxicity, intracardiac catheters.
2. **Sustained VT**

   Patient HD unstable – DC cardioversion with 50 J. If ineffective 150 J, and if needed 250 J. After conversion to sinus rhythm Lidocaine infusion at rate of 2-4 mg/min.

   Patient HD stable – Lidocaine bolus 1 mg/kg IV. Repeat after 10 min. if no reversal to sinus rhythm. After reversion prophylactic lidocaine drip at rate of 2–4 mg/min. If lidocaine fails – (ii) Mexiletine 100–150 mg IV at rate of 25 mg/min for 3 h, then maintenance infusion of 0.5 mg/min. (iii) If DC shock, lidocaine and mexiletine fail – correction of factors that potentiate the arrhythmia (hyperkalaemia, metabolic acidosis, hypoxia) if present and 20–40 mEq of potassium chloride in 5% dextrose infusion can be tried.

   If no response to above regime and in presence of hypotension or fast pulse rate – Amiodarone IV bolus 300 mg followed by infusion of 1.2 g over 24 h, or Bretylium tosylate 5–10 mg/kg IV over 20 min. Repeat 100 mg every 10 min till total dose of 500 mg. Maintenance dose 100 mg q8h. In refractory cases not responding to antiarrhythmic drugs – Magnesium sulphate 2 g stat IV, followed by infusion containing 8 g of the drug.

   If failure to convert by DC shock or antiarrhythmic drugs – Trial of programmed electrical stimulation of ventricles, or overdriving of ventricles through transvenous pacing catheter introduced into RV.

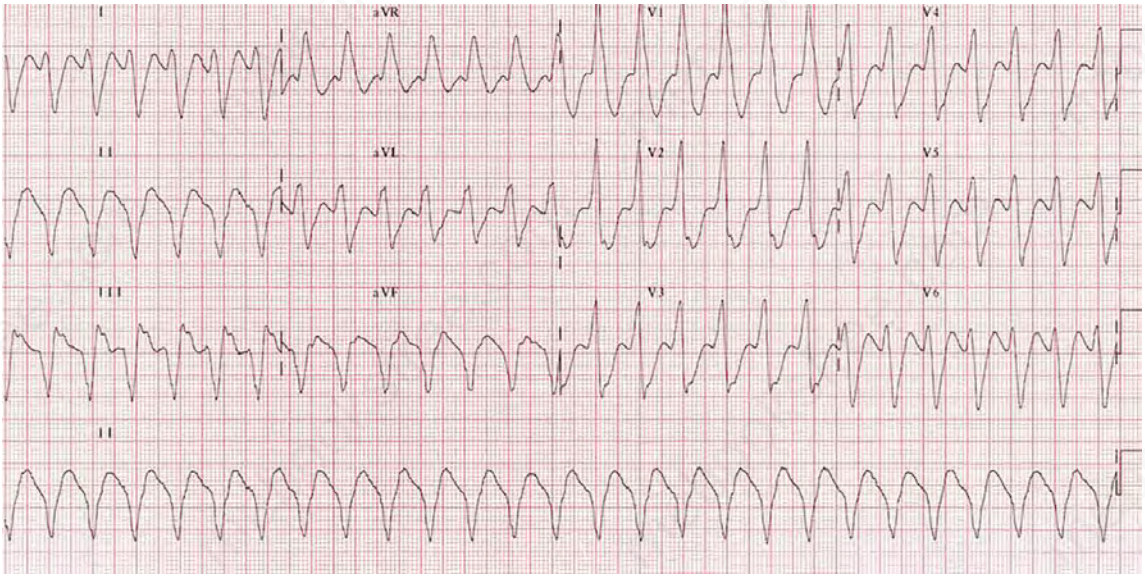


Fig. 25: 12-lead ECG showing ventricular tachycardia

Table 23: ECG features of ventricular tachycardia

• Abnormal wide complexes
• QRS > 0.12 second
• Extreme axis deviation
• Fusion or capture beats
• Chest lead concordance
• Right bundle branch block morphology with Rsr' in V1 or qS in V6

Prophylaxis (Long-term Treatment)

1. Management of underlying heart disease such as heart failure and maintenance of serum electrolytes within normal range.
2. Drugs – Amiodarone or Sotalol.
3. Radiofrequency catheter and surgical ablation–for some patients with stable monomorphic VT.
4. Automatic implantable cardioverter/defibrillator (AICD). *Indications*—
   - Survival of an episode of ventricular fibrillation or hypotensive VT in absence of acute MI.
   - Incomplete suppression of the arrhythmia by antiarrhythmic drugs, as determined by electrophysiologic testing, stress testing, or ambulatory ECG recording.
   - Patients with symptoms of syncope not documented by VT (or VF) during EP testing but who demonstrate inducible VT or VF during EP testing and do not respond to drugs.

Working – The AICD pulse generator is implanted subcutaneously in paraumbilical area. If a malignant tachyarrhythmia occurs, the AICD recognises it within 5–15 sec. and then delivers the shock. This results in termination of the arrhythmia in most cases.

Other Types of VT

NON-SUSTAINED VT – At least 6 consecutive impulses lasting up to 30 sec. Danger of sustained VT in patients with advanced IHD or cardiomyopathy. Treatment same as with other forms of PVCs.

REPETITIVE MONOPHASIC VT – A benign disturbance; paroxysms may be separated by only one sinus beat. Occasionally turn into sustained VT. No treatment unless associated structural heart disease.

TORSADES DE POINTES (Cardiac ballet or pre-fibrillary VT) – Polymorphic VT which occurs as a proarrhythmic response to Class IA or at times Class C antiarrhythmic agents. Also complete AV block, hyperkalaemia and tricyclic antidepressants, or as part of congenital prolonged QT syndrome, transient myocardial ischaemia, thrombolytic therapy or Prinzmetal's angina.

ECG – Characteristic variation in axis of QRS complexes causing an undulating or 'twisted' appearance (Fig. 26).

Treatment is of underlying cause. Overdrive atrial or ventricular pacing may be necessary.

Re-entry tachycardias Most cardiac arrhythmias are generated by a depolarization wave form which

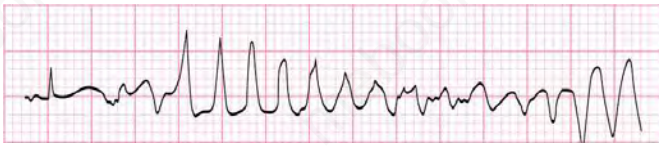


Fig. 26: *Torsades de pointes*

repetitively circulates around an area of block to conduction. A common example is the AV re-entry tachycardia (AVRT) seen in WPW syndrome.

Intracardiac electrophysiology, Catheter Ablation and Implantable Cardioverter Defibrillators

Interventional therapies of catheter ablation and the implantable cardioverter defibrillator have been increasingly applied in the management of cardiac arrhythmias.

Catheter ablation represents a natural progression of EPS from a diagnostic procedure to therapy. Successful treatment of an arrhythmia by ablation depends on establishing the arrhythmia mechanism and localizing the arrhythmogenic area of myocardium (mapping). This area is then destroyed without damage to the surrounding tissue (ablation).

Table 26 lists complications and management of ablation.

Computer mapping systems allow complete mapping of the arrhythmia substrates. Alternative forms of energy development may be cooled. tip RF delivery, laser cryothermy, ultrasound and microwave frequencies.

Indications and targets for ablation

See Table 27 for details of ablation in various types of arrhythmias.

Implantable defibrillators

An implantable cardiac defibrillator (ICD) automatically detects an arrhythmia and delivers either overdrive pacing therapy or a DC shock to terminate it. ICDs are implanted in a subpectoral pouch (Fig. 27).

HEART BLOCK

Types

1. Sino-atrial
2. Atrioventricular block at division of bundle of His.
3. AV block at level of bundle branches.

SINO-ATRIAL BLOCK

A condition in which the SA node initiates an impulse but there is a block to the exit of the impulse from the SA node to the atria.

Diagnosis

- Intermittent pulse, halving of cardiac rate or long pause depending on frequency of dropped beats.
- Abolished by exercise or atropine.
- ECG – Pause with complete absence of PQRST. P-P interval twice the dominant P-P interval (Fig. 29).

Table 24: Differential diagnosis of regular tachycardia

	Sinus tachycardia	*Supraventricular tachycardia*	*Ventricular tachycardia*	*Atrial flutter with 2:1 block*
Onset and termination	Gradual	Sudden	Sudden	May be sudden
Heart disease	Absent	Often absent	Usually present	Usually present
Heart rate	Rarely more than 160	160 or more	160 or more	Usually 150
Jugular venous pulse				
(a) Rate compared to ventricular rate	Same	Same	Difficult to distinguish	Ventricular rate half the rate of flutter waves
(b) Cannon waves	Absent	Regular cannon waves	Irregular cannon waves may be seen	Regular cannon waves may be observed
1st heart sound	Constant	Constant	Variable intensity	Constant
Carotid sinus	Gradual slowing with gradual return to previous rate on release of pressure	No change or abrupt reversion to normal	No change	Abrupt slowing for few beats only

Table 25: Differential diagnosis of irregular tachycardia

	Multiple ectopic beats	*Atrial fibrillation*	*Atrial flutter (with varying block)*	*Sinus arrhythmia (with tachycardia)*
Associated condition	Idiopathic, ischaemic heart disease, digitalis toxicity, etc.	Rheumatic heart disease, thyrotoxicosis, ischaemic, or hypertensive heart disease, or none	Same as in A. fibrillation	Normal heart Common in children
Rate at apex	Usually less than 120	More than 120	About 160	Less than 140
Effect of exercise	Disappear	Rhythm becomes more irregular	May become regular	Disappear
Pulse apex deficit	May be present	Marked	None	None
Heart sounds	Occasionally only 1st sound heard	Vary in intensity	Variation of 1st heart sound	Normal
Other features	Long pauses preceded by premature beats. Irregular cannon waves in jugular pulse	Pauses without preceding premature beats. More often permanent	Jugular pulse shows flutter waves. More often paroxysmal	Rhythm becomes regular if breath is held

Table 26: Complications of ablation

Complication	*Treatment*
Heart block	Permanent pacemaker
Tamponade	Percutaneous drainage and reversal of heparin
Hematoma and false aneurysm	May require surgical repair
Thromboembolism (effects usually transient)	Anticoagulation, aspirin

Management – (i) Treatment of cause – e.g. digitalis intoxication. (ii) Pacing for rare cases in which there is prolonged asystole and Stokes-Adams attacks.

ATRIOVENTRICULAR BLOCK

I. ***First degree block – Prolonged PR interval.***

Causes – See Table 28.

Table 27: Indications and targets for ablation

Arrhythmia	*Substrate*	*Frequency*	*Region targeted*
Atrioventricular nodal reentry tachycardia	Two insertions to the compact atrioventricular node	About 70% of regular supraventricular tachycardias	Slow pathway (lower complication and higher success) or fast pathway (higher risk of atrioventricular block)
Accessory pathway	Anywhere around atrioventricular junction, 65% left free wall, 25% septal, 10% right free wall	10% of regular supraventricular tachycardias	The accessory pathway
Atrial flutter	Rotation around the right atrial free wall and between the tricuspid valve and the inferior vena cava isthmus in a clockwise (common) or anticlockwise direction	10% of regular supraventricular tachycardias	Tricuspid valve and inferior vena cava isthmus
Atrial fibrillation	Many re-entry circuits throughout both atria	4% of adult population	Curative: Still not determined Palliative: Atrioventricular node
Ventricular tachycardia	Re-entry around scar (usually left ventricle secondary to ischaemia)	84% of referrals	Diastolic potentials
	Bundle branch re-entry	6% of referrals	Right bundle
	Idiopathic (focus in right ventricular outflow tract in 70%)	10% of referrals	Right ventricular outflow tract

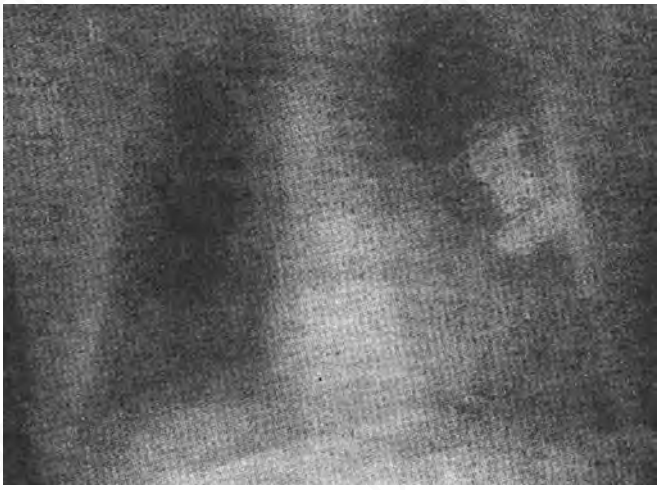


Fig. 27: A posteroanterior radiograph of the chest of a patient with a pectorally implanted defibrillator. The lead can be seen passing through the left subclavian vein to the right ventricular apex. Two defibrillation coils can be seen on the lead

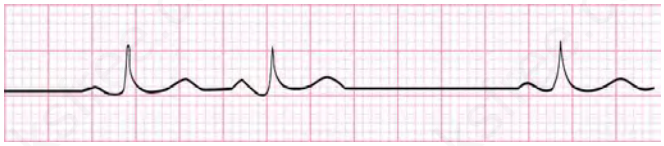


Fig. 29: S-A block. A complete PQRST complex is omitted and the P-P interval is twice the normal length

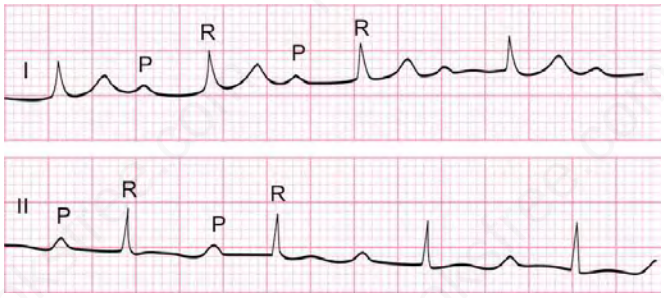


Fig. 30: First degree heart block. P-R interval almost 0.4 second

Diagnosis

1. Pre-systolic triple rhythm – Atrial systole is so far removed from ventricular systole that it becomes audible.
2. S_1 diminished in intensity.
3. Definite interval between presystolic murmur and first sound at apex if mitral stenosis.

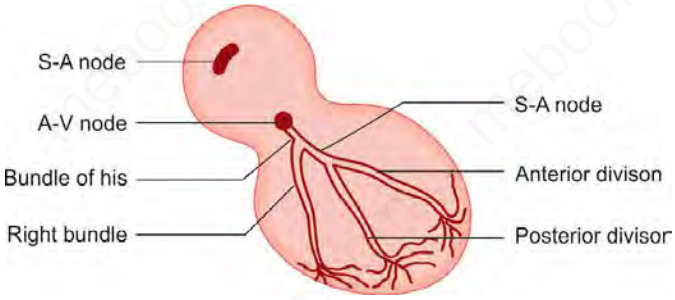


Fig. 28: Conducting system of the heart

Table 28: Causes of first degree heart block
Acute rheumatic fever
Inferior myocardial infarct
Myocarditis, e.g. diphtheritic
Degenerative myocardial disease
Drugs – Digitalis, β-blockers, calcium antagonists, emetine
Hyperkalaemia
Congenital heart disease (ASD)
Increased vagal tone (in normal individuals)

4. Prolongation of AV conduction may be judged if 'a' waves visible in the neck on one side and carotid pulsation palpated on other side.
5. Cannon waves in the neck if PR interval is so prolonged that P falls between QRS and T of the previous cycle.
ECG – PR interval more than 0.2 sec. (Figs. 30 and 31).
Treatment – No specific therapy is required.

II. ***Second degree block (Partial heart block)***

Causes

- Acute rheumatic fever, diphtheria.
- Ischaemic heart disease.
- Digitalis toxicity
- Viral infections.

Types of Partial Heart Block

1. **Mobitz type I (Wenckebach phenomena)** – Gradual lengthening of PR interval until a P wave is not followed by a QRS complex, the cycle then starts again, (Figs. 32 and 33). As AV conduction worsens, less impulses are transmitted in each cycle and then Wenckebach period shortens. Ultimately 2:1 AV block may occur.
Recognised at bedside by – (a) Occurrence of dropped beat without preceding premature beat. (b) Intensity of 1st sound may be constantly faint or it may decrease in intensity over several beats.

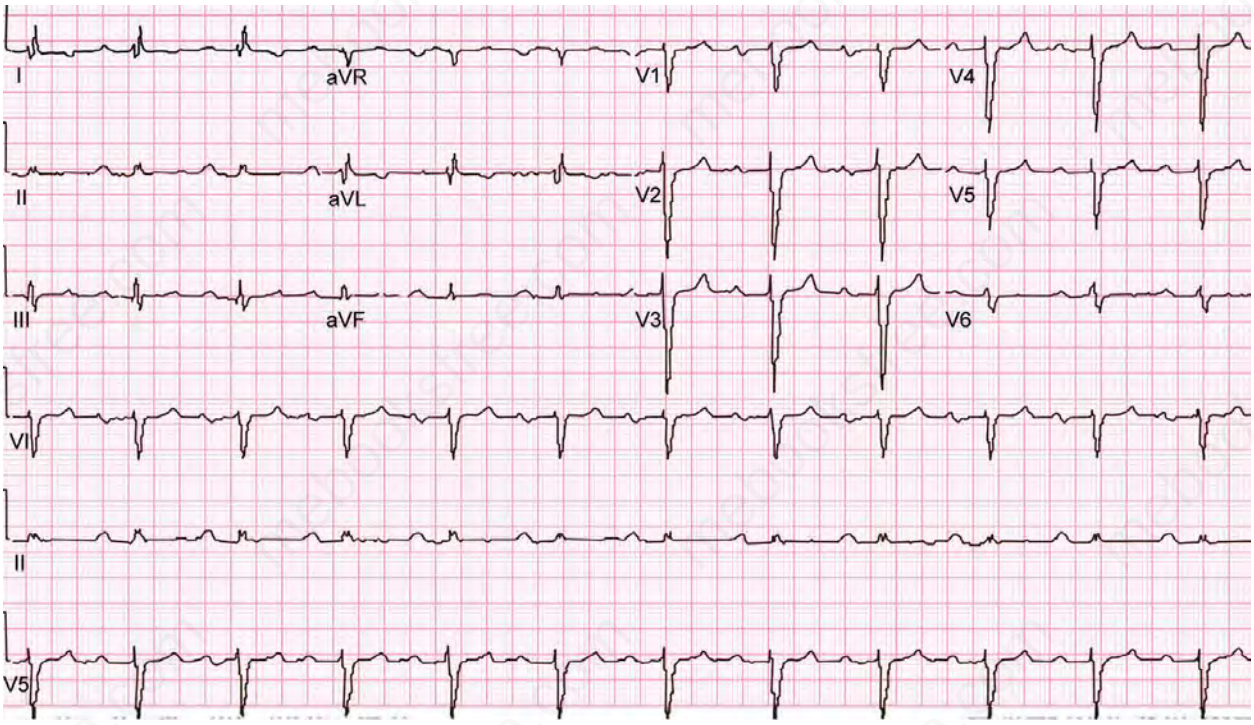


Fig. 31: 12-lead ECG showing first degree AV block

In regular 2:1 or 3:1 block, it may be impossible to distinguish between a high or Mobitz type I block and a low or Mobitz type II block on standard ECG, but the site of lesion can be localised by His bundle electrogram.

Treatment – A stable arrhythmia which rarely requires permanent pacing.

2. **Mobitz type II (Intermittent type)**
   - Regular rhythm with sudden pauses slightly less than two normal cycles.
   - Small atrial waves may be seen in the jugular vein during these pauses.
   - ECG – PR interval remains constant but QRS complexes are dropped out intermittently (Fig. 34).

3. **Fixed type**–Ventricles respond to every second (Figs. 35 and 36) third or fourth beat –2:1, 3:1, 4:1, block, but the PR interval remains constant. When the conduction is 3:1 or 4:1 the block is termed high grade AV block.

   Signs – Pulse slow and regular. Neck veins show pulsations of atrial origin at a rate of two, or three, or four times faster than the radial pulse rate.

   Treatment – Since it may progress to complete heart block, permanent pacing indicated to prevent symptomatic episodes.

III. ***Third degree block (Complete heart block)***
CAUSES: See Table 29.

Symptoms

- *Due to low cardiac output* – Lassitude, fatigue, lightheadedness, and especially during exercise syncope. Symptoms of vertebrobasilar insufficiency and congestive heart failure may be precipitated.
- *Due to increased stroke volume* – Uncomfortable awareness of heart beat, or slow palpitation if block is intermittent.
- *Due to transient circulatory arrest* – Stokes-Adams attacks – Symptoms depend on duration of standstill of circulation: About 5 seconds – giddiness and faintness, about 10 seconds – convulsions. Convulsions and incontinence may suggest epilepsy, but in transient asystole pallor is often striking, patient flushes during recovery, and consciousness is regained very rapidly, though some permanent impairment of cerebral function may occur after long or repeated episodes.

Signs

- *Slow and regular heart rate* – at 30 to 50 beats per minute, which does not usually increase significantly with physical activity or exercise.
- *Raised JVP* – 'a' waves may be seen in the neck unrelated to ventricular beats.

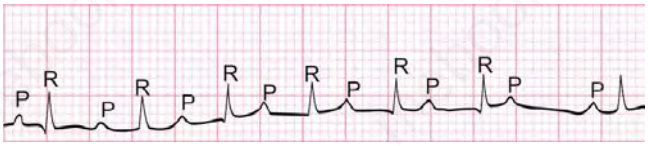


Fig. 32: Wenckebach second degree AV block. Progressive lengthening of PR interval followed by dropped QRS. A junctional escape beat delays the start of the next sequence

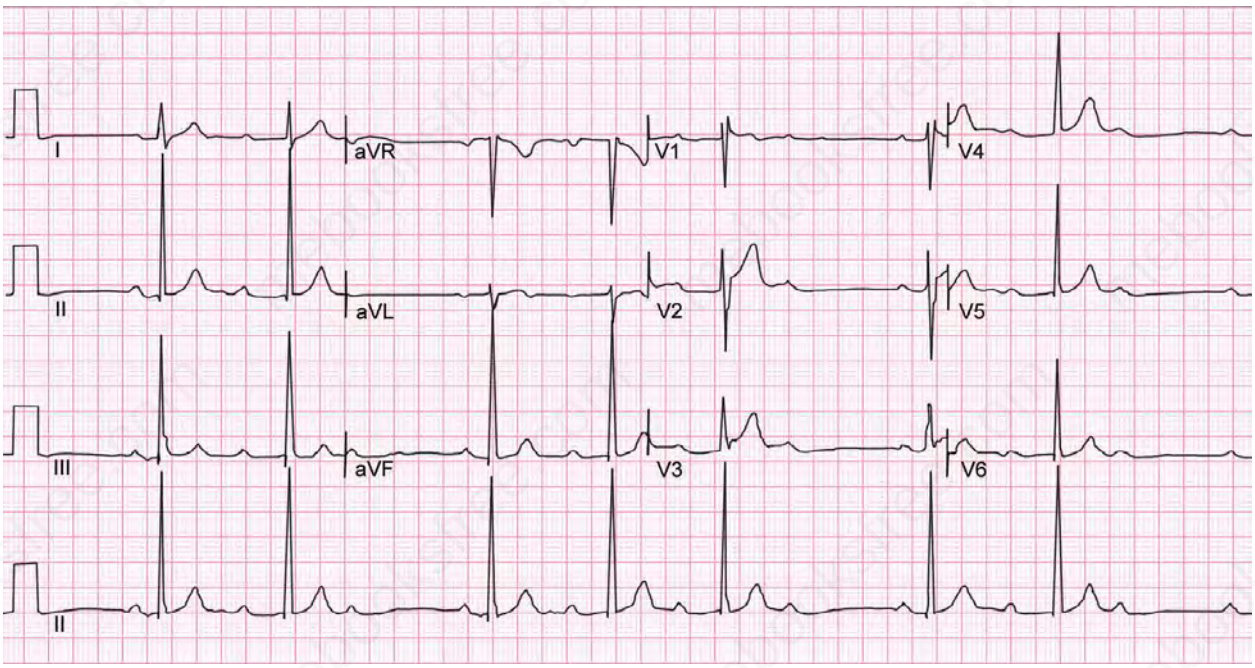


Fig. 33: Mobitz type 1 2nd degree AV block. Serial prolongation of PR interval till one P wave is not followed by a QRS complex

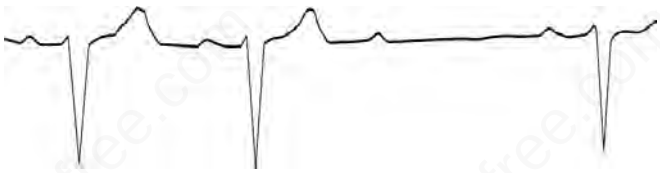


Fig. 34: Mobitz type II AV block

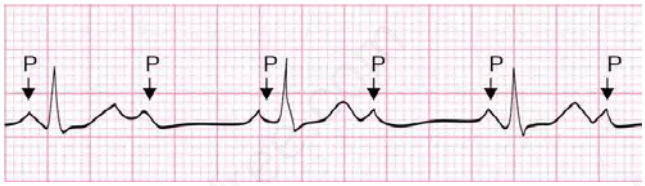


Fig. 35: 2:1 AV block

- *Cannon waves* – Giant 'a' waves which are transmitted to the neck when the atrium contracts against a closed tricuspid valve.
- *Variation in intensity of 1st heart sound* – 1st sound is loudest when the interval between the preceding atrial beat and the ventricular beat is short, it is faintest when the interval is long. From time to time, there is a sharp accentuation of the 1st sound at the apex (cannon sound).
- *Wide pulse pressure* – due to increased systolic pressure and low diastolic pressure. This gives rise to water hammer pulse and capillary pulsation.
- *Cardiac enlargement* – due to increased stroke volume. Hyperdynamic cardiac impulse.
- *Systolic ejection murmur* – loudest in 2nd and 3rd left interspaces adjacent to the sternal edge, and due to increased velocity of blood flow associated with increased stroke volume.
- *Atrial sounds* – may be heard in inconstant relation to 1st and 2nd heart sounds.
- *Apical diastolic flow murmur* – occasional.
- *ECG* (Figs. 37 and 38) – No relation between atrial and ventricular complexes. The duration of QRS is normal.

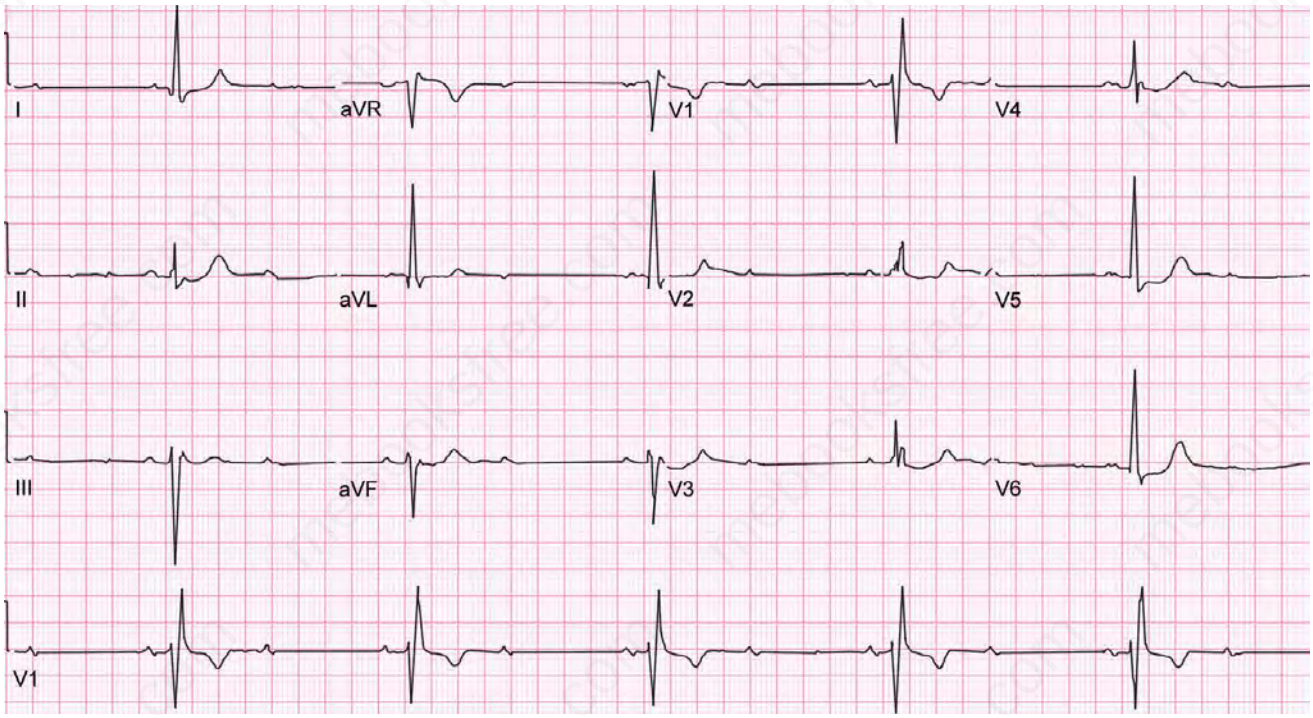


Fig. 36: 12-lead ECG showing 2:1 AV Block

Table 29: Causes of third degree heart block

Congenital
Usually associated with VSD, rarely isolated.
Acquired
• Rheumatic heart disease
• Acute infections – Rheumatic fever, diphtheria.
• Drugs – Digitalis, quinidine
• Calcific aortic stenosis.
• Trauma (penetrating).
• Surgical procedures – After correction of VSD, or following insertion of prosthetic valves or removal of hypertrophied septum in hypertrophic cardiomyopathy.
• Cardiomyopathy (particularly infiltrative).
• Syphilitic heart disease.
• Infiltrative masses – Sarcoidosis, tubercles, abscesses from endocarditis, gummas, tumors, amyloidosis, haemochromatosis.
• Collagen diseases – Rheumatoid arthritis, dermatomyositis.
• Fistulae – Sinus of Valsalva aneurysm rupturing into right atrium.
• Unknown cause – Idiopathic fibrosis.

High block – QRS of normal pattern and duration and with ventricular rate between 40-50/min. Low block – Wide QRS complex and rate 20-40/min.

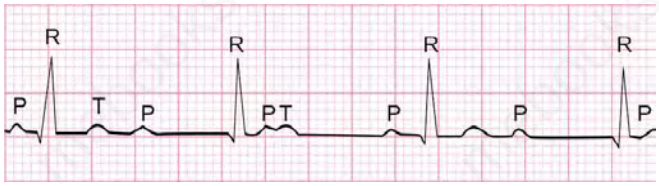


Fig. 37: Atria and ventricles depolarize independently. QRS complexes less frequent; regular at 40 to 55/minute

Differential Diagnosis

(a) *Of bradycardia* (See Table 30).

(b) *Of AV dissociation (with interference)* – Here the atrial impulses are not conducted to the ventricles because the AV node is still within its normal refractory period. It may occur as slowing of normal pacemaker activity or acceleration of a subordinate focus, or in presence of complete AV block (See Table 31).

Treatment of complete heart block:

1. Drugs – (i) *Isoprenaline* – 2.5 mg in 500 mL dextrose as IV infusion accelerates the heart rate in most patients. Rate of infusion adjusted to keep heart rate between 70–100/min (ii) *Atropine* – Block associated with inferior infarction is usually transient and may be reversed by 0.5–1.2 mg IV atropine.

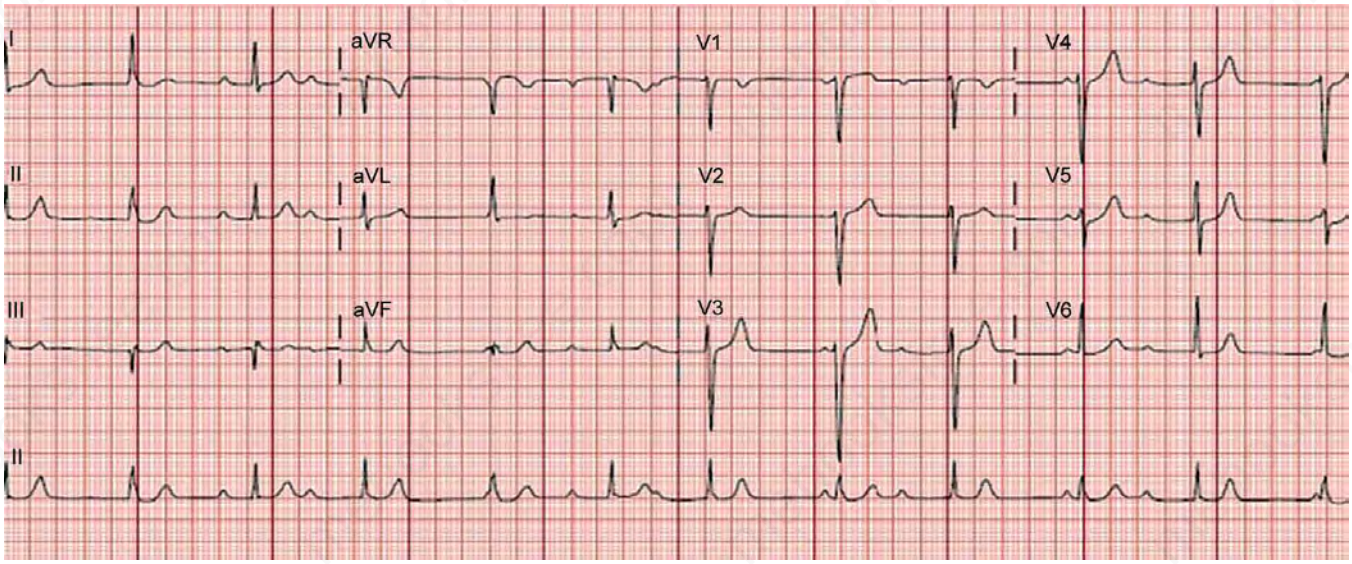


Fig. 38: 12-lead ECG showing complete heart block (CHB)

Table 30: Differential diagnosis of Bradycardia

	Sinus bradycardia	*Partial heart block (high grade)*	*Complete heart block*	*Sino-atrial block*	*Junctional rhythm*
Incidence	Fairly common	Common	Common	Very rare	Very rare
Heart rate	40–60	40 or less	40 or less (except congenital, in children or due to digitalis)	About 40	About 50–60
Associated condition	Athlete heart, increased intracranial tension, jaundice, myxoedema	Coronary disease rheumatic fever, or diphtheria, digitalis	Same as partial heart block	Increased vagal tone, digitalis, beta-blocking agents, coronary disease, diphtheria	Digitalis intoxication
Jugular venous pulsations	Normal 'a' waves preceding carotid impulse	Atrial waves more than ventricular rate	Position of 'a' waves continually changes with periodic cannon waves	No waves during pause in heart sounds	Cannon waves may be seen
Effect of exercise, atropine or emotion	Increase in rate	Abrupt slowing	No change or slight increase	May disappear	No change
Carotid sinus pressure	Further slowing, especially if sensitive carotid sinus	Further slowing	No effect	Further slowing	May result in atrial standstill with persistent ventricular action
Heart sounds	Constant	No irregular change Atrial sounds may be heard	Changing intensity of S_1. Cannon sounds may be heard. Atrial sound may be audible	Constant	S_1 may be intensified due to simultaneous atrial and ventricular contraction

Table 31: Differential diagnosis of AV dissociation

	Complete AV block	*AV dissociation*
Cause	Acute infarction, digitalis, cardiomyopathy, congenital	Digitalis, myocarditis or myocardial infarction.
Syncope	Common	Uncommon
Duration	Often permanent	Usually transient
ECG		
Atrial rate	Usually faster than vent. rate	Usually slower than vent. rate
Vent. rate	About 40/min.	Usually above 60/min
QRS complex	Supravent. or vent.	Usually supravent
P falling after T	May occur	Does not occur

Table 32: Indications of pacing

Temporary cardiac pacing—
• Symptomatic complete or incomplete heart block unresponsive to medical therapy.
• Acute myocardial infarction complicated by significant conduction defect and/or tachyarrhythmia which causes cardiovascular collapse and is unresponsive to medical therapy.
Permanent cardiac pacing—
• Symptomatic bradyarrhythmia, e.g. sick sinus
• Intermittent Mobitz type II A-V block documented on Holter monitor.
• Alternating RBBB and LBBB.
• Acquired complete heart block if symptomatic
• Symptomatic congenital heart block.
• Drug resistant tachyarrhythmias.
• Atrial fibrillation with bradycardia and pauses >5 s

Table 33: Indication for pacemaker in acquired AV block

1 . Third-degree or high grade AV block at any anatomic level associated with—
(a) Symptomatic bradycardia
(b) Essential drug therapy that produces symptomatic bradycardia
(c) Periods of a systole >3 s or any escape rate <40 beats/min while awake, or an escape rhythm originating below the AV node
(d) Postoperative AV block not expected to resolve
(e) Catheter ablation of the AV junction
(f) Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy and peroneal muscular atrophy, regardless of the presence of symptoms
2. Second-degree AV block with symptomatic bradycardia
3. Type II second-degree AV block with a wide QRS complex with or without symptoms
4. Exercise induced second or third-degree AV block in the absence of ischemia

2. Pacing – *Indications*

See Tables 32 and 33 for the indications of pacing.

For emergency treatment of Adams-Stokes attacks—See cardiac arrest.

C. Intraventricular block

1. Bundle branch block

Delay in the spread of excitation through the ventricle whose bundle is blocked so that QRS interval is prolonged to 0.12 sec or longer. See Table 34 for the causes and diagnosis of right and left bundle branch block.

Table 34: Causes and diagnosis of bundle branch block

RBBB	*LBBB*
Causes	
Physiological	IHD
IHD	Hypertension
Cong. heart dis.	Aortic valve disease
e.g. ASD	Cardiomyopathy
RV hypertrophy	
or strain e.g.	
pulmonary embolism	
Diagnosis	
Wide splitting of S_2	Reversed splitting of S_2
ECG: Wide QRS,	ECG: Broad and
S wave in lead I,	slurred QRS complexes,
R in V_1 (Fig. 39)	qs wave in V_1 (Fig. 40)

2. Fascicular block (Hemiblock)

A hemiblock is when one of the two fascicles of the left bundle fails to conduct. Unless there is associated RBBB, total duration of QRS complex is not grossly prolonged.

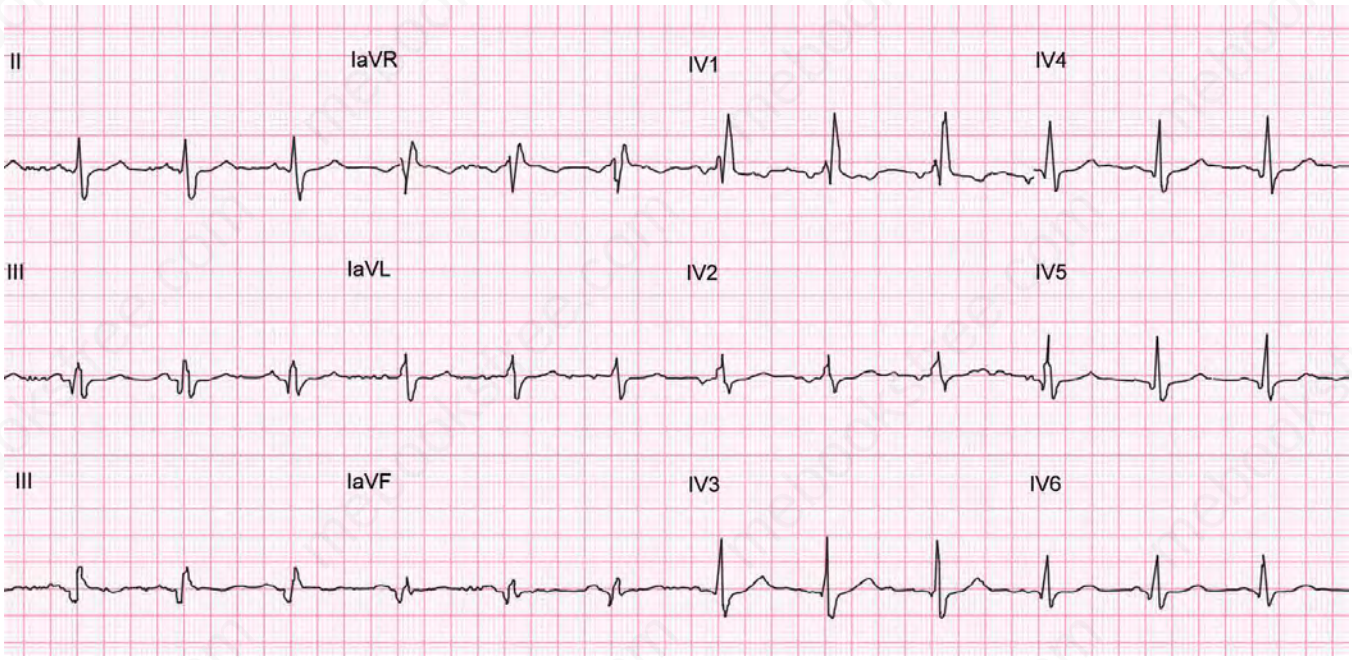


Fig. 39: 12-lead ECG showing right bundle branch block (RBBB)

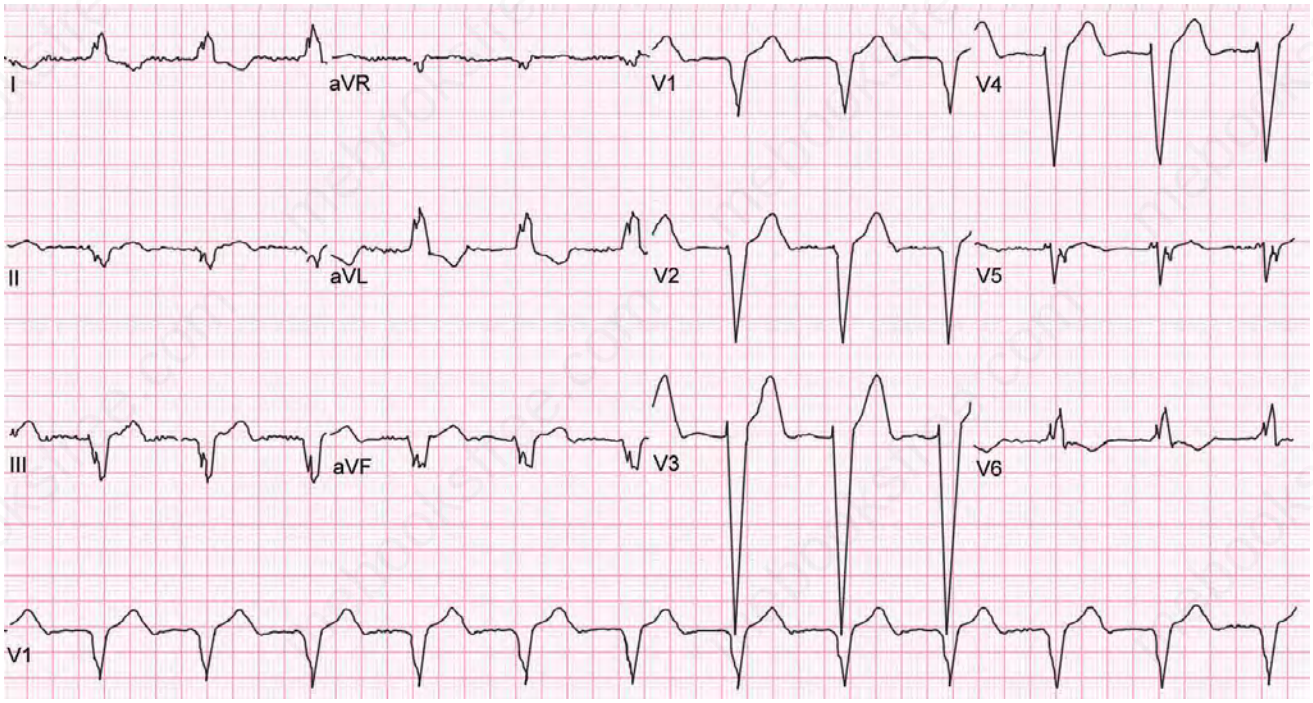


Fig. 40: 12-lead ECG showing left bundle branch block (LBBB)

Left anterior fascicular block – is associated with left axis deviation >-30° (predominantly negative deflections in leads II, III).

Posterior fascicular block – is associated with gross right axis deviation (predominantly negative lead I and positive lead III).

Bifascicular block – Failure of conduction in two of the divisions causes RBBB with LAD, or complete LBBB.

Trifascicular block - Block in all three fascicles would result in complete heart block.

Indications for pacemaker implantation in chronic bifascicular and trifascicular block:

1. Intermittent third-degree AV block
2. Type II second-degree AV block
3. Alternating bundle branch block

4. CARDIAC MURMURS

CLASSIFICATION

I. Innocent – Associated with no known abnormality either structural or physiologic.

II. Physiological – Murmurs caused by disturbance in the physiology of the circulation, e.g. those related to hyperkinetic state or overactive circulation – excitement, anaemia, fever, thyrotoxicosis, pregnancy, cor pulmonale, portal hypertension and beriberi heart disease.

III. Relative or functional – Murmurs caused by structural disorders not involving valves or abnormal cardiac or vascular communications – murmurs caused by dilatation of heart chambers or dilatation of vessels.

IV. Organic – Murmurs caused by valvular disease, shunts or narrowed vessels.

SYSTOLIC MURMURS

I. **Innocent systolic murmurs**
- Soft. Never more than grade 2–3
- Short
- Heard over limited area of precordium.
- Increase in volume with tachycardia, and decrease or disappear when heart rate slows.
- Vary with respiration, either increasing or decreasing in volume with inspiration.
- Always systolic in time (except venous hum) but never diastolic.
- Vary with posture and may disappear completely on valsalva manoeuvre.
- Chest radiograph and ECG are normal.

Types

(a) *Vibratory murmurs* – Short, early systolic murmur, best heard down left sternal edge and sometimes towards apex. Of musical or twanging quality, it is best heard with child lying down, is less loud in erect posture and disappears when he extends his neck and arches his back.

(b) *Pectus excavatum* – Many of these patients will have an innocent systolic murmur due to slight distortion of underlying structures by the deformity.

(c) *Straight back syndrome* – The normal anterior concavity of vertebral column in upper dorsal region is absent. This reduces the anteroposterior diameter of the thorax, and so the heart is compressed between the spine posteriorly and sternum anteriorly. Distortion of the outflow tract and great vessels leads to production of a systolic murmur in pulmonary area.

(d) *Pulmonary systolic murmur* – Soft systolic murmur best heard in second left intercostal space close to the sternum. It becomes louder with tachycardia and hyperkinetic states, and may disappear on inspiration.

(e) *Cardio-respiratory murmur* – May be produced by compression of lung segment by the left ventricle. Heard best at apex. Changes in posture and respiration produce changes in intensity and character of murmur.

(f) *Isolated carotid bruit* – is louder in supraclavicular fossa and over the carotids than in the aortic area; it may be associated with a faint thrill that is often abolished by head movement.

II. **Physiological systolic murmurs** – Associated with hyperkinetic or high output states such as exercise, fever, pregnancy. Ejection systolic murmur best heard in the pulmonary area and along the left sternal border. Ejection sound may be heard. Loud first sound. Wide pulse pressure. Venous hum and S_3 often heard.

III. **Functional systolic murmurs**

(a) ***Ejection systolic***

1. *Aortic or pulmonary ejection flow murmur* – Causes – (i) Increased volumes due to shunt flows, e.g. ASD, VSD, PDA. (ii) Increased stroke volumes due to regurgitant leaks such as aortic and pulmonary regurgitation. (iii) Increased cardiac outputs (innocent murmur) as in thyrotoxicosis, anaemia, exercise, pregnancy, and systemic arteriovenous fistulae. (iv) Increased stroke volume due to marked bradycardia as in complete AV block. (v) A narrow anteroposterior chest diameter (straight back syndrome). The loss of thoracic kyphosis in this condition produces a pulmonary ejection murmur.
2. *Aortic ejection murmur in the elderly* – About 50% over age of 50 have audible aortic ejection murmur without valve stenosis. May be due to fibrous aortic valves which do not fully open, or calcific spurs which protrude into the aortic stream when calcium is laid down at the roots of the cusps, or turbulence in the ascending aorta due to atherosclerotic plaque.

Table 35: Differences between organic and functional MR

	Organic MR	*Functional MR*
Murmur		
Intensity	Harsh and loud	Soft and blowing
Duration	Pansystolic	Of short duration. Often late systolic
Radiation	To left axilla or to aortic area	Little radiation Murmur may vary in intensity with change of position
Sounds	1st sound obscured by murmur. 3rd heart sound may be heard. P_2 may be accentuated	1st sound normal. 3rd heart sound not heard. Mid or late systolic clicks common
Thrill	Systolic thrill with very loud murmurs	No thrill
Cause	Rheumatic fever	LV enlargement due to hypertension, myocardial infarction, etc.
Associated MS	Often present	No
Persistence of murmur	Murmur does not disappear with treatment	Murmur may disappear with improvement of circulatory status

3. *Ejection murmur due* to *flow into a relatively dilated chamber* – (i) Idiopathic or secondary dilatation of pulmonary artery. (ii) Dilatation of ascending aorta as in aneurysm or pulmonary atresia.

(b) ***Pansystolic***

1. *Mitral regurgitation* – Due to left ventricular dilatation from any cause – hypertension, ischaemia, aortic valve disease.
2. *Tricuspid regurgitation* – Any condition giving rise to RV dilatation or failure e.g. pulmonary hypertension, high output states, pulmonary stenosis, atrial fibrillation.

IV. **Organic systolic murmurs**

(a) ***Mid systolic***

1. *Aortic stenosis* – Ejection systolic murmur. Loud, harsh, best heard in second right interspace. Aortic second sound diminished or absent. Systolic thrill in aortic area. Anacrotic pulse.
2. *Pulmonary stenosis* – Loud, harsh, ejection systolic murmur in pulmonary area. P_2 soft and delayed or absent. Systolic thrill in pulmonary area.
3. *Fallot's tetralogy* – The murmur is due to pulmonary stenosis. The right ventricle has two exits so that more severe the stenosis, less the pulmonary flow and shorter the murmur.
4. *Atrial septal defect* – Systolic murmur heard over second and third left interspace. The murmur is due to increased flow of blood across the pulmonary valve and not to the shunt through the septal defect. Wide and fixed split of 2nd sound. Systolic thrill sometimes.
5. *Bicuspid aortic valve* – A soft mid-systolic murmur in aortic area preceded by an ejection click at the apex indicates bicuspid valve without significant obstruction.

(b) ***Pansystolic***

1. *Mitral regurgitation* – Loud blowing pansystolic murmur best heard at apex. Radiates to axilla and posteriorly. 1st sound normal or soft. A 3rd sound may be heard in severe cases, and a systolic thrill may be felt (Table 35).
2. *Tricuspid regurgitation* – Pansystolic, harsh blowing murmur loudest in tricuspid area. Murmur increases in intensity during inspiration. May be accompanied by palpable thrill.
3. *Ventricular septal defect* – Murmur depends on size of defect. With mild to moderate defect pansystolic murmur best heard in third or fourth left interspace. Systolic thrill.
4. *Persistent ductus arteriosus* – (i) In infants and young children, where the systemic blood pressure is relatively low only a systolic murmur is heard in the pulmonary area. (ii) With the gradual development of pulmonary hypertension, the typical continuous murmur may be replaced by a systolic murmur only.

(c) ***Late systolic***

1. *Coarctation of aorta* – The following systolic murmurs may be heard – (i) Aortic ejection murmur produced by blood flow across normal aortic valves and often found in hypertension. When valve stenosis is present, the murmur is loud and radiates more widely. (ii) Systolic murmur due to collaterals – Murmur of varying intensity and widely distributed over collaterals both anteriorly and posteriorly. (iii) Systolic murmur due to coarctation over the site of stricture.

2. *Hypertrophic obstructive cardio-myopathy* – Murmur maximal at lower sternal border or apex. Murmur of mitral regurgitation often superimposed. Ejection systolic click never heard. Diastolic murmur of aortic regurgitation never present. Fast rising pulse. Ascending aorta seldom dilated on X-ray.
3. *Mitral valve prolapse* – Billowing or prolapse of one or both leaflets into left atrium during systole. Late systolic murmur, often musical and often associated with single or multiple clicks. On standing the click and murmur may become earlier, and in some patients a curious whoop or honking noise may be heard in systole. When the posterior leaflet is ballooning, the main stream of turbulence is anterior towards the left sternal edge and into the carotids (as in AS). When the anterior cusp is ballooning, the murmur is often radiated round to the thoracic spine.
4. *Disease of the mitral chordae* – An abnormal mitral valve with elongated chordae may become incompetent during the course of systole. There is usually a mid-systolic click initiating the murmur which runs upto the second sound. A similar situation may occur in case of papillary muscle dysfunction following myocardial infarction.
5. *Pulmonary arterial stenosis* – In case of severe PS, the pulmonary systolic murmur is loud with its peak in late systole. It is accompanied by a systolic thrill and an early or absent ejection click and the murmur does not increase in intensity on expiration.

(d) ***Early systolic*** – Early systolic murmur at lower left sternal border always represents a closed or virtually closed VSD, acute MR, TR with normal pulmonary artery pressure.

DIASTOLIC MURMURS

Functional diastolic murmurs

1. *Mitral* – Due to increased flow across mitral valve – (i) Left-to-right shunts (VSD, PDA), gross mitral incompetence, hyper-kinetic state, e.g. thyrotoxicosis. Shorter than murmur of organic MS, no presystolic component and usually starts with S_3. (ii) Austin Flint murmur.
2. *Tricuspid* – (i) Due to increased flow across tricuspid valve – ASD, partial or total anomalous pulmonary venous drainage, MR, TR, Ebstein's anomaly, severe anaemia, hyperthyroidism, pulmonary hypertension and cor pulmonale. (ii) With gross pulmonary regurgitation (Austin Flint murmur on the right side).

Table 36: Differences between AR and functional PR

Aortic regurgitation murmur	*Graham Steell murmur*
1. Other evidences of rheumatic heart disease	1. Evidence of pulmonary hypertension
2. Systolic murmur of aortic stenosis heard	2. No systolic murmur of AS
3. Wide transmission of murmur	3. Murmur not widely transmitted
4. Murmur may be louder during expiration	4. Murmur louder during inspiration
5. P_2 not loud	5. P_2 loud
6. Peripheral signs of aortic regurgitation	6. No peripheral signs
7. CXR — pulmonary artery normal	7. Large pulmonary artery

3. *Pulmonary* – Graham Steell murmur due to pulmonary hypertension, e.g. in MS (Table 36).

Organic diastolic murmurs

(a) ***Early***: Regurgitation across semilunar valves

1. *Aortic regurgitation* – Soft or loud early diastolic murmur. High pitched and blowing, best heard along left sternal border. Associated soft ejection systolic murmur. In AR, the loudness is as much due to anatomy of the aortic valve as the degree of regurgitation. Calcified or rheumatic valves usually produce loud murmurs, while aortic dilatation produces soft murmurs.
2. *Pulmonary regurgitation* – Uncommon condition. Character same as AR murmur. Site of maximum intensity in pulmonary area and more limited radiation. May result from infective endocarditis or surgery, or idiopathic dilatation of pulmonary artery with dilatation of valve ring.

(b) ***Mid or late:*** Obstruction at AV valves

1. *Mitral* stenosis – Accentuated and snapping apical first sound. Low pitched, rumbling diastolic murmur with presystolic accentuation in the established case. Murmur localized to the apex. Opening snap of the mitral valve.
2. *Tricuspid stenosis* – Mid-diastolic murmur with presystolic accentuation, loudest at lower sternal edge. Murmur tends to be accentuated during inspiration. No presystolic crescendo. Opening snap.
3. *Carey Coombs murmur* – Soft low pitched mid-diastolic apical murmur due to active rheumatic valvulitis. Murmur usually disappears after acute attack.

4. *Myxoma of left atrium* – Murmur variable from time to time. Delayed mitral valve closure gives rise to split 1st sound, early systolic murmur, late diastolic sound (tumour click) and a short mid-diastolic murmur.

(c) ***Late:*** Austin Flint murmur of AR, presystolic accentuation of MS.

CONTINUOUS MURMURS

1. **Shunt between blood vessel of cardiac chamber of high pressure to one of low pressure:**
   (i) *Intracardiac* – Rupture of sinus of valsalva to right atrium, right ventricle or rarely pulmonary artery. The continuous murmur is heard maximally at lower left sternal border and has a diastolic accentuation.
   (ii) *Extracardiac* – PDA, aortopulmonary septal defect, pulmonary AV fistula, coronary AV fistula. Blalock-Taussig shunt.
2. **Blood flow across severely narrowed vessel** – Coarctation of aorta, aortic arch arteritis, pulmonary arterial stenosis, pulmonary atresia, Fallot's tetralogy.
3. **Increased velocity of blood flow through normal dilated vessels.**

Physiological (Innocent continuous murmurs)
See Table 37.

Table 37: Physiological continuous murmurs

Venous hum
• Soft blowing murmur that starts in systole and continues through second sound into diastole.
• Heard in some children at the root of the neck or just below the clavicle on either side but more commonly on the right.
• Can be abolished by pressure on the jugular vein or by making the patient lie down flat.
• Increases in inspiration when the venous return to the heart is increased.
• Differs from murmur of PDA in lacking any machinery quality.
Mammary souffle
• Continuous high pitched murmur with diastolic accentuation may be heard in last trimester of pregnancy and for 4–6 weeks in the post-partum period.
• Usual site along left sternal border
• Firm pressure with the stethoscope or with the finger lateral to the stethoscope, where the murmur is heard, gently obliterates it.
• May disappear when patient sits up.
Pathological
• Bronchial collateral circulation with severe obstruction to pulmonary artery flow.
• An A-V fistula, either pulmonary artery to pulmonary vein or internal mammary to adjacent vein.
• Large subcostal collaterals in coarctation of aorta.

5. CONGENITAL HEART DISEASE

AETIOLOGY

1. Sex—*Females:* ASD, PDA, more common. *Males:* Coarctation, transposition of great vessels, aortic arch disease.
2. Causes of congenital heart disease

See Table 38 for the causes of congenital heart disease.

CLASSIFICATION

I. ***Without intracardiac shunt (Acyanotic)***

Dextrocardia – The heart lies within the right thorax. Types:

(a) *Isolated dextrocardia* – due to incomplete rotation of the heart around its long axis. The left chambers lie to the left and anteriorly, the right chambers to the right and posteriorly.

(b) *True dextrocardia* – with mirror-like transposition of the heart. There is a similar mirror-type transposition of the other viscera (situs inversus). Usually no other congenital cardiovascular defects. Mirror-image X-ray picture. ECG – Mirror image of normal pattern.

Obstructive lesions

Coarctation of aorta. Discrete narrowing of aortic arch just below the ductus (post-ductal in 90%) or just above the ductus (pre-ductal–more severe) due to deformity of the wall.

History – Presentation with severe heart failure in second week of life (pre-ductal type) related to constriction of ductus arteriosus.

Symptoms – With mild degree of aortic obstruction no symptoms or symptoms due to complications.

SIGNS

1. *Murmurs:*
   Systolic –
   Aortic from dilatation of aorta
   Of coarctation between scapulae
   Over collaterals
   Of AS

Table 38: Causes of congenital heart disease

Cause	*Defect*
Maternal	Patent ductus
rubella	ASD PS
Drugs	
Alcohol	VSD
Lithium	Tricuspid atresia Ebstein's anomaly
Genetic	
Single gene defects	
Noonan's syn.	Hypertrophic cardiomyopathy Pulmonary stenosis ASD
Marfan's syn.	Aortic root dilatation (and potentially aortic dissection) Mitral valve prolapse
Holt-Oram syn.	ASD
	VSD (occasional)
Chromosomal defects	
Down's syn.	ASD VSD Fallot's tetralogy Patent ductus
Edward's syn.	VSD
Patau's syn.	ASD, PDA (occasional)
Turner's syn.	Coarctation Bicuspid aortic valve Pulmonary stenosis
Lesions associated with 22q11 deletions	Truncus arteriosus
	Interrupted aortic arch Fallot's tetralogy Pulmonary atresia with VSD VSD Absent pulmonary valve syn. Anomalous origin of pulmonary artery Right aortic arch Coarctation Vascular ring

Diastolic –

Of AR

Mid-diastolic murmur at apex (due to thickening of mitral valve)

Continuous–over collaterals.

2. *Evidence of compensatory collateral circulation* – Dilated and tortuous internal mammary, intercostal and scapular arteries (Suzman's sign).

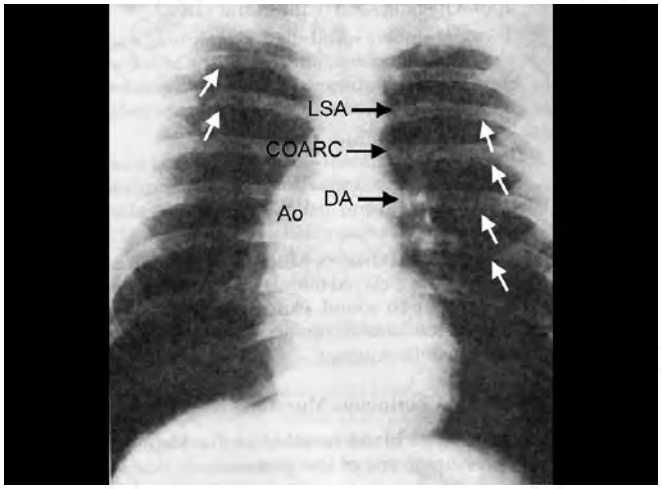


Fig. 41: Coarctation of aorta. Arrows point to sites of notching on the undersurface of the posterior ribs

3. *BP* – moderately high, and much less in lower extremities compared to upper.
4. *Weak femoral pulsations and radio-femoral delay.*
5. *Signs of LV hypertrophy.*
6. *Carotid 'swell'* – Excessive carotid and subclavian pulsation and suprasternal pulsation.
7. *'Corkscrew' retinal vessels.*

INVESTIGATIONS

Chest radiograph

- Small or absent aortic knob.
- Figure 3 configuration of aortic shadow formed from above down by pre-stenotic dilatation, coarctation itself and post-stenotic dilatation (Figs. 41 and 42). Reverse or inverted 3 sign on barium swallow produced by the same mechanism.
- Dock's sign – Notching of ribs due to pressure of dilated intercostal arteries. Notching is bilateral in juxta-ductal type of coarctation.

ECG – LV hypertrophy develops progressively with age.

Echo – Interruption of aortic arch distal to left carotid, left subclavian or left innominate (most common to least common) and post-stenotic dilatation of aorta (Fig. 43).

Cardiac catheterization – Significant systolic pressure difference across coarctation. Angiography will demonstrate site and length of coarctation.

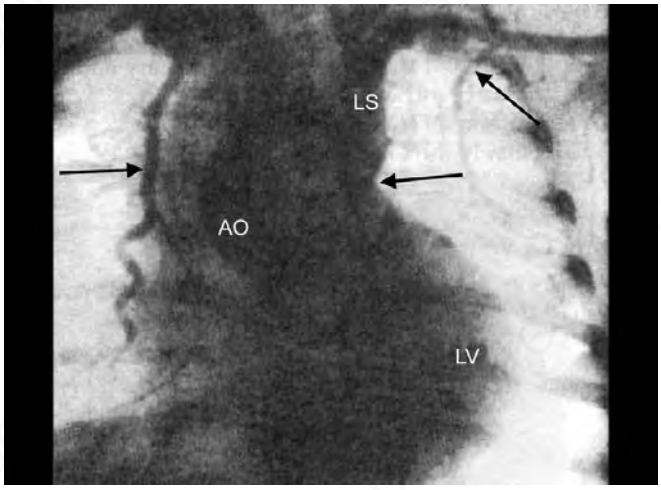


Fig. 42: Aortogram of a child, a case of coarctation of the aorta, distal to the left subclavian artery (LS). AP view with arrows pointing to the well-developed collateral circulation

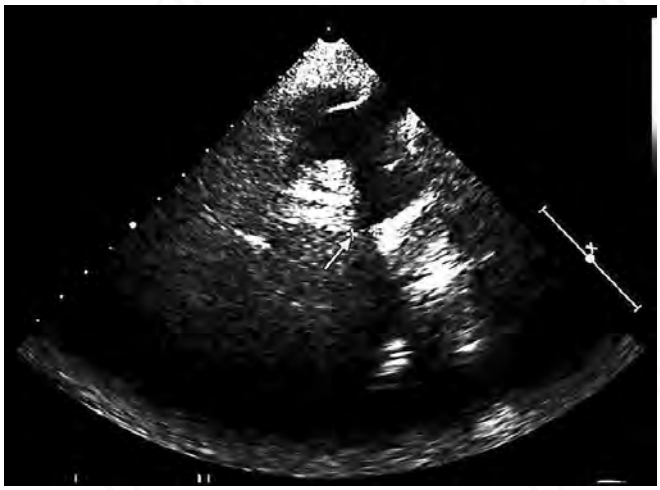


Fig. 43: Echocardiography showing coarctation of aorta (arrow)

MRI and IV DSA – can demonstrate area of coarctation and collaterals.

Associated Anomalies:

1. Bicuspid aortic valve; AR may result
2. Persistent ductus arteriosus
3. Ventricular septal defect
4. Marfan's syndrome, Noonan's syndrome
5. Anomalous origin of subclavian artery
6. Floppy mitral valve
7. Congenital cerebral berry aneurysms

Complications:

1. Aortic rupture with or without dissection
2. Infective endocarditis.
3. Heart failure in presence of fibroelastosis at birth.

Aortic stenosis: Occurs at subvalvar, valvar or supravalvar level. Supravalvar AS is associated with William's syndrome. Turner's syndrome is associated with AS and coarctation.

(For Clinical features and Diagnosis, see Valvular heart disease).

Pulmonary stenosis:

History: Mostly asymptomatic in childhood. If severe stenosis, right heart failure.

Signs: Depend on degree of stenosis –

- *Systolic thrill* in pulmonary area.
- *Systolic murmur* over 2nd and 3rd left intercostal space. Murmur is louder and longer the more severe the stenosis.

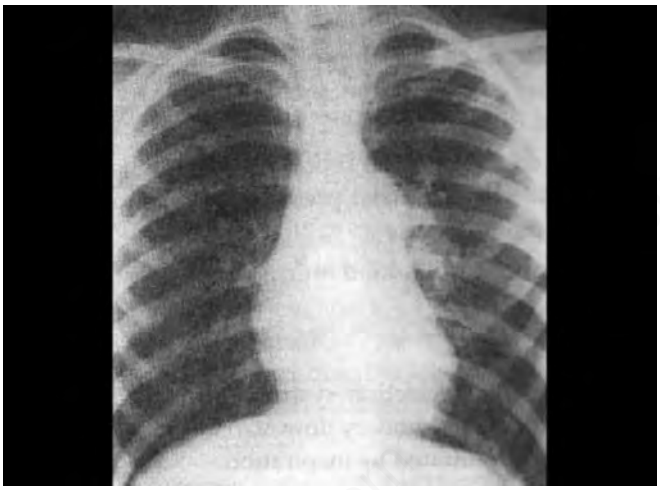


Fig. 44: Chest X-ray of a patient with severe pulmonary stenosis showing post-stenotic dilatation of pulmonary trunk and left pulmonary artery

- *Systolic ejection click* (not in severe stenosis).
- Both A_2 and P_2 heard in mild cases, P2 diminishes as the stenosis becomes more severe.
- 'a' wave seen in the neck.
- Right ventricular heave.
- Right atrial presystolic gallop in severe cases.
- Moon-shaped face and peripheral cyanosis with severe stenosis.

INVESTIGATIONS

Chest radiograph (Fig. 44)

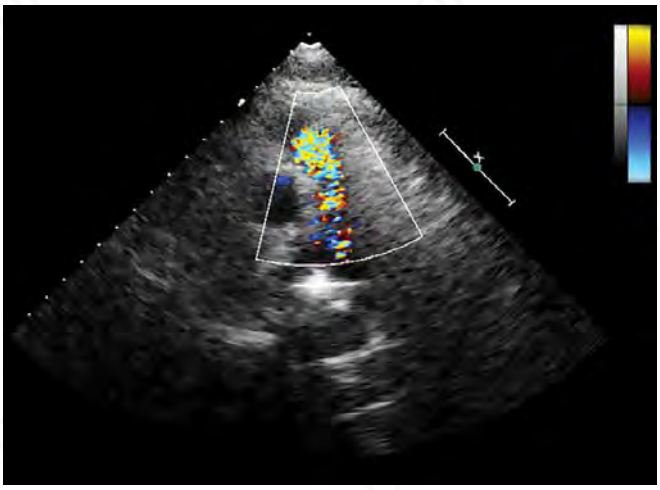


Fig. 45: 2D echo Doppler in severe pulmonary stenosis

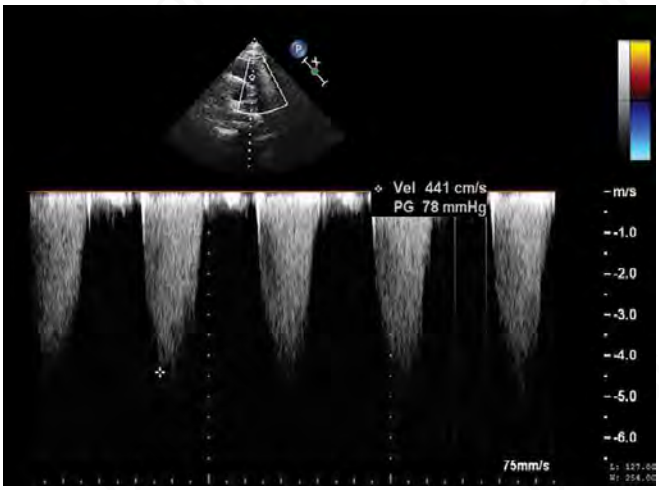


Fig. 46: Echocardiography in severe pulmonary stenosis

- Enlargement of RA and RV
- Post-stenotic dilatation of pulmonary artery.
- Oligaemic lung fields.

ECG – RV preponderance with P pulmonale.

Echo – Pulmonary valve thickening. Turbulent mosaic flow on colour flow mapping and gradient estimation across the thickened valve is best accomplished by continuous wave Doppler interrogation (Figs. 45 and 46).

Cardiac catheterization – Elevated RV systolic pressure with low pressure in pulmonary artery.

ASSOCIATIONS

- Rubella syndrome – Valvar and peripheral pulmonary artery stenosis.
- Pulmonary valve abnormalities may be associated with
  - Noonan's syndrome: Dysplastic valves.
  - Williams' syndrome: Supravalvar PS with supravalvar AS.

COMPLICATIONS

- Atrial fibrillation
- Infective endocarditis

LEFT-TO-RIGHT SHUNTS (ACYANOTIC)

ATRIAL SEPTAL DEFECT

Opening in interatrial septum due to deficiency in septal tissue.

Types of defects in order of frequency:

Secundum type: In central portion of septum.

Primum defect: Immediately above AV valves and often associated with CLEFT in anterior mitral valve leaflet. More common in females.

Sinus venosus type: Near orifice of SVC often associated with anomalous pulmonary venous drainage.

History: Asymptomatic in children. Symptoms of fatigue and dyspnoea may occur in adults.

Signs

- Visible and palpable RV.
- 1st sound often accentuated and split with loud tricuspid component. May be preceded by loud atrial systolic murmur.
- Wide fixed splitting of S_2 – Wide because of delay in RV ejection, increased stroke volume and RBBB.

Fixed because the septal defect equalises the right and left atrial pressures throughout the respiratory cycle.

- Systolic thrill if loud murmur.
- Ejection click.
- Murmurs –
  - Pulmonary ejection systolic murmur due to increased pulmonary flow. Variable in intensity and accentuated by inspiration.
  - Tricuspid flow murmur – Mid-diastolic murmur near left sternal edge louder on inspiration.
  - Graham Steell murmur of pulmonary regurgitation if pulmonary hypertension.
  - Late systolic murmur (mitral valve prolapse associated with secundum ASD)
  - Murmur of mitral incompetence (with primum defect).

  - Mitral stenosis murmur (Lutembacher's syndrome)
  - Murmur of tricuspid incompetence–Pulmonary hypertension, primum defect, Ebstein's anomaly (with secundum defect).
- Small peripheral pulse – because of reduced LV output.
- Atrial fibrillation or flutter may precipitate heart failure.

Investigations

Chest radiograph (Fig. 47):

- Dilation of trunk of pulmonary artery and its larger branches.
- Absence of LA enlargement.
- Hilar dance on fluoroscopy.

ECG: Incomplete RBBB.

Echo: Drop-out in area of interatrial septum. Doppler colour flow imaging defines atrial septal defect flow as well as other intracardiac shunts (Figs. 48 to 53).

Catheterization: High saturation in RA. RV and pulmonary artery because of blood flow from left to right.

Associated Lesions

1. Lutembacher's syndrome – Associated MS.
2. Pulmonary stenosis.
3. Anomalous pulmonary venous drainage.
4. Holt-Oram syndrome – Skeletal deformities of forearm.

Complications

1. Pulmonary hypertension.
2. Reversal of shunt (Eisenmenger's syndrome).
3. Infective endocarditis – rare except with ostium primum defect or PS.

VENTRICULAR SEPTAL DEFECT

Opening in ventricular septum that permits communication between the two ventricles.

History: Infants with large defects develop heart failure. In about 70% of cases defects are small, and in about 60% these close spontaneously, and many more become so small that they are clinically insignificant.

Signs

Small defects – (Maladie de Roger) – Loud pansystolic murmur and thrill maximum in fourth left intercostal space.

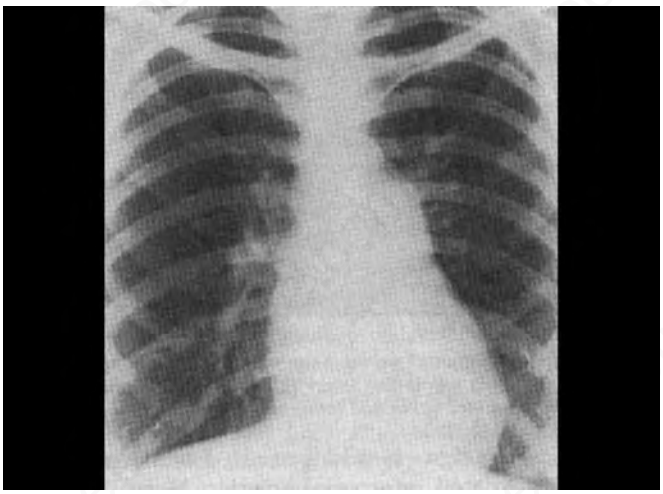


Fig. 47: Atrial septal defect. Cardiac enlargement mainly of RV, prominent pulmonary outflow tract and large main pulmonary arteries and lobar arteries

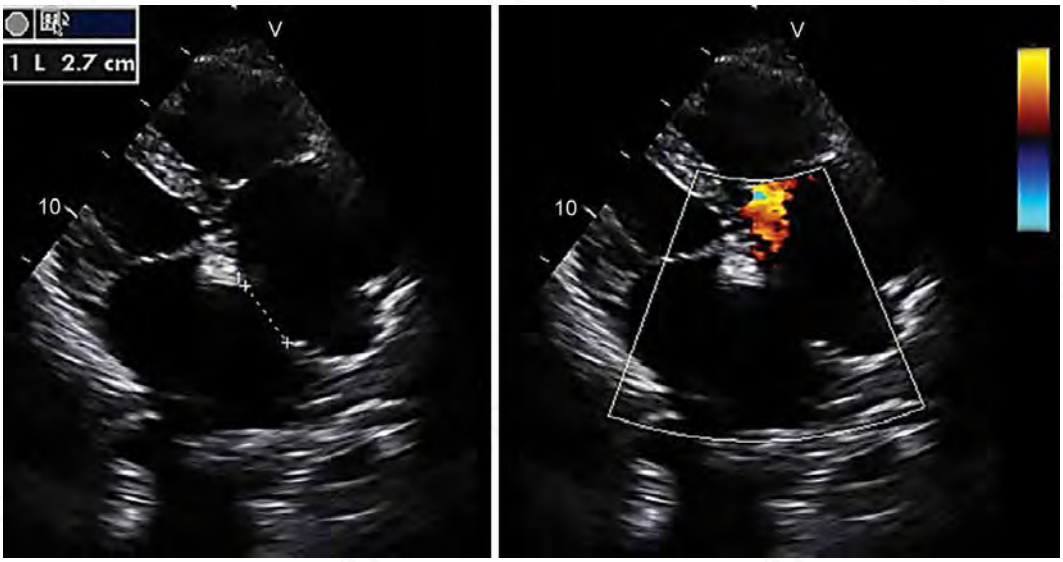


Fig. 48: 2D echo apical four-chamber view showing a large ostium secundum ASD

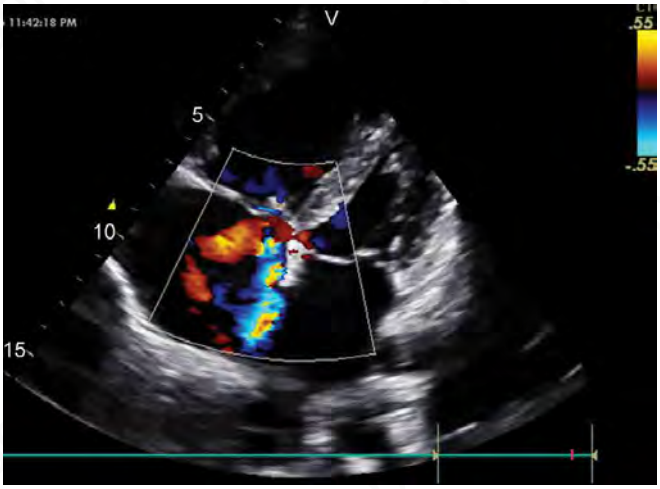


Fig. 49: 2D echo showing a large ostium secundum ASD. Blue colour is the TR jet. Red-flow across ASD

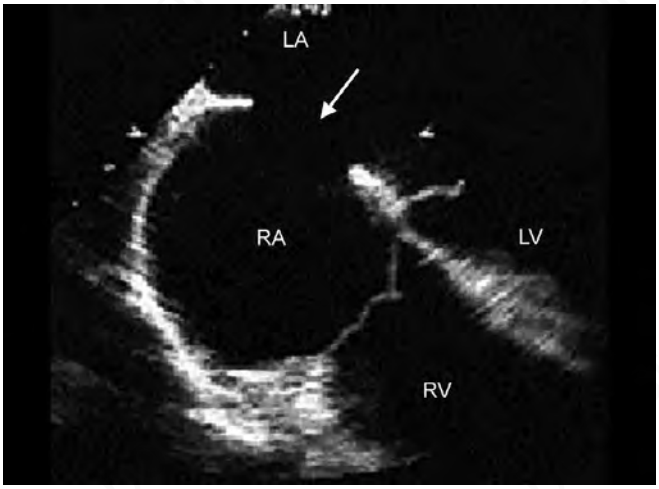


Fig. 50: ASD before closure (arrow)

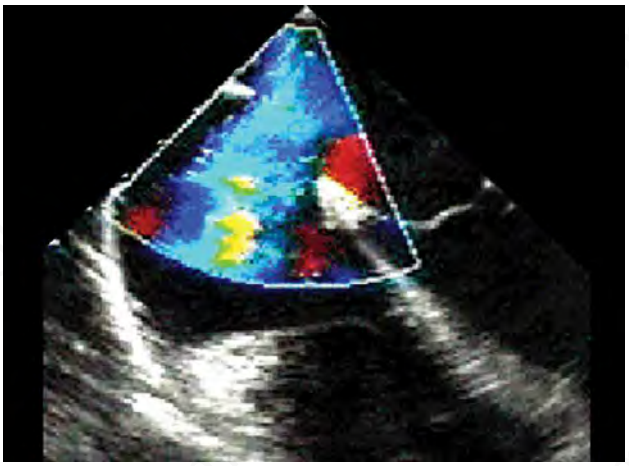


Fig. 51: ASD before closure showing flow across ASD

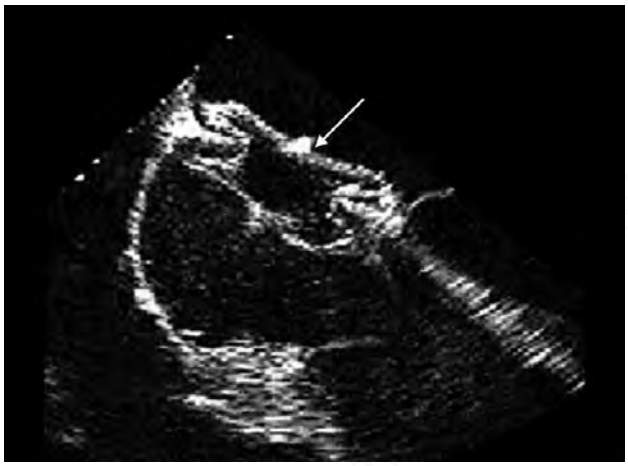


Fig. 52: ASD immediate after closure (arrow)

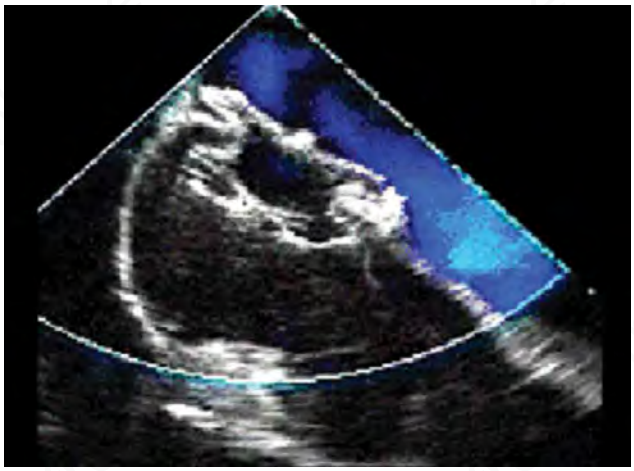


Fig. 53: ASD after closure showing cessation of flow

S_2 normal and widely split due to delay in onset of RV systole.

Medium and Large Defects

- Pansystolic murmur at left sternal edge, less loud than murmur of small defect, due to flow from high pressure LV to low pressure RV during systole.
  - A large defect may produce a soft murmur particularly if pressure in RV is elevated. This may be immediately after birth while pulmonary vascular resistance remains high, or when the shunt is reversed.
- Mitral diastolic flow murmur.
- P_2 accentuated and Graham Steell murmur if pulmonary hypertension.

- Hyperkinetic LV thrust and left parasternal heave if large shunt.
- Loud S_3 because of rapid LV filling.

INVESTIGATIONS

- *X-ray:* Normal if small defect, cardiomegaly and pulmonary plethora if large defect (Fig. 54).
- *ECG:* Normal if small defect. With large defect biventricular and RA hypertrophy.
- *Echo:* Imaging of defect and shunt pattern across it by colour flow mapping (Figs. 55 to 57).

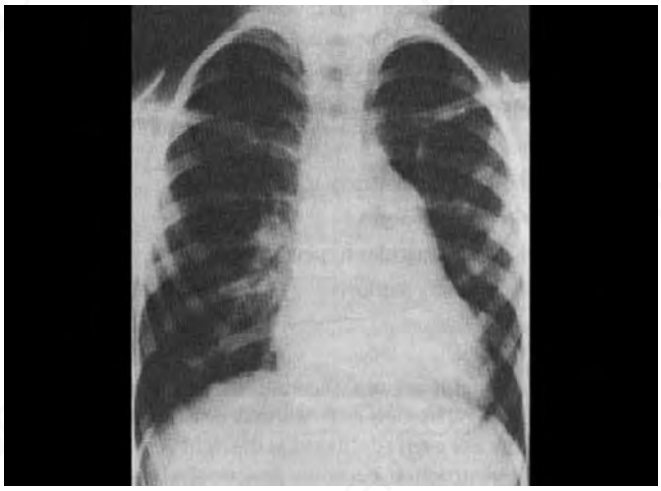


Fig. 54: X-ray of a chest of ventricular septal defect with moderate shunt, increase of pulmonary blood flow

ASSOCIATED LESIONS

- Aortic regurgitation.
- Complete heart block.
- Subacute infective endocarditis.
- Eisenmenger's complex.

PERSISTENT DUCTUS ARTERIOSUS

Patency of the foetal vessel that connects aorta and pulmonary artery.

History

Patency of ductus is common in preterm infants, and spontaneous closure usually occurs. If ductus is small, and pulmonary pressure normal, survival, without symptoms, into adult life is possible.

Signs

- Gibson murmur – Continuous murmur loudest towards end of systole and early diastole (machinery or train in tunnel murmur), accentuated during expiration. With development of pulmonary hypertension, first the diastolic murmur disappears because of equalization of diastolic pressures in pulmonary artery and aorta, then the systolic murmur shortens until only a short ejection murmur persists. If the shunt becomes reversed the murmur disappears.
- Continuous thrill in pulmonary area.
- P_2 accentuated.

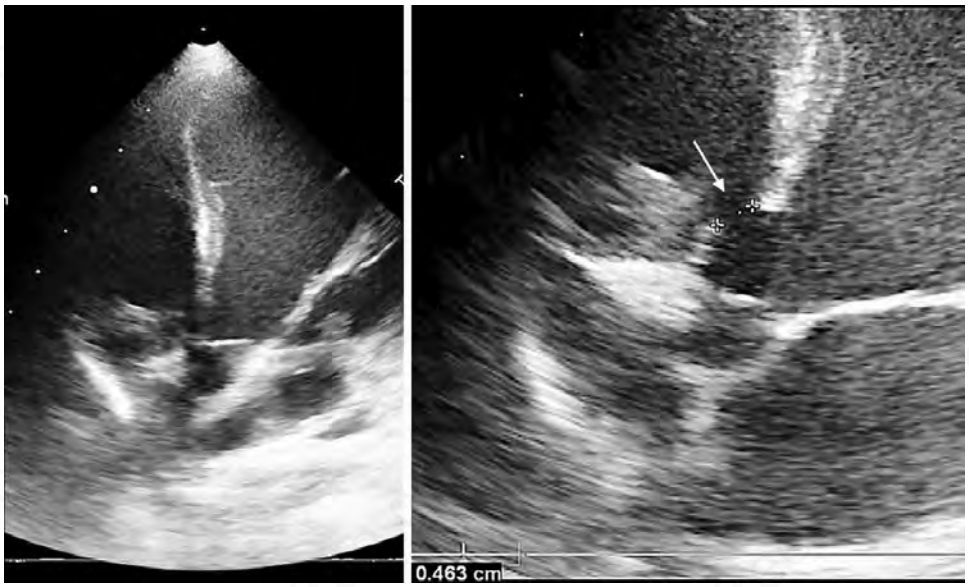


Fig. 55: 2D echo showing ventricular septal defect (arrow)

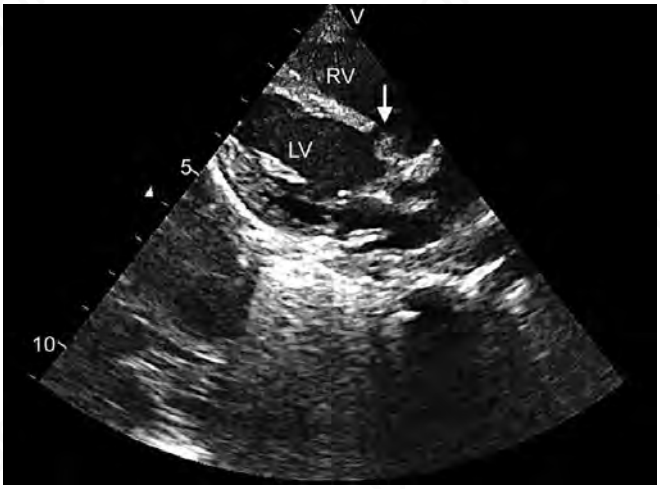


Fig. 56: 2D echo showing a VSD (arrow) in the high muscular septum

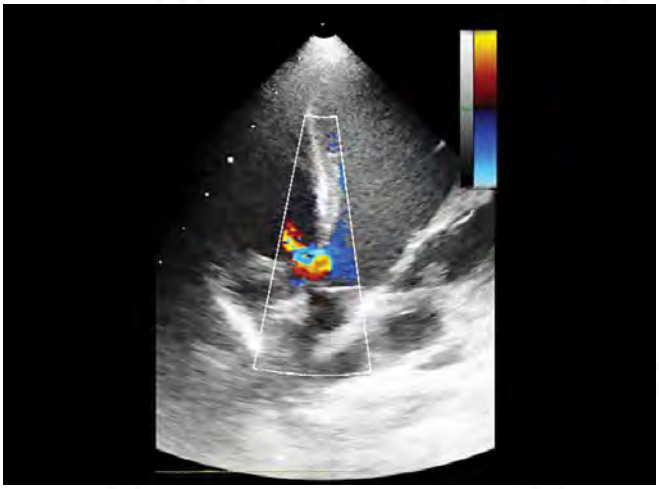


Fig. 57: Echo Doppler showing flow across ventricular septal defect

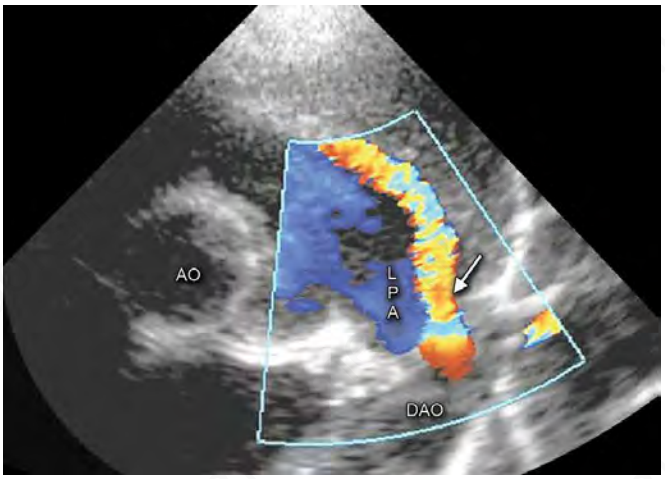


Fig. 58: Two-dimensional echocardiography in high parasternal view (ductal view) with color flow mapping showing patent ductus arteriosus (PDA; arrow) with left-toright shunt. (AO: Aorta; DAO: Descending thoracic aorta LPA: Left pulmonary artery; PDA: Patent ductus arteriosus)

- Single second sound or even reversed splitting if ductus is large because of prolonged LV systole from volume overload of LV.
- Mid-diastolic mitral flow murmur.
- Aortic ejection systolic murmur not uncommon but often masked by the continuous murmur.
- Collapsing pulse if large shunt.
- Pulsations in suprasternal notch.
- Low diastolic pressure. Exercise causes transient drop in diastolic pressure (Bohn's sign).
- LV type of cardiac impulse.
- Differential cyanosis – Upper part of body including arms less cyanosed than lower part of body if duct distal to left subclavian artery. Right hand less cyanosed than the left hand and feet if proximal.

Investigations

X-ray – Pulmonary plethora proportional to degree of left-to-right shunt, LV enlarged and aortic knuckle prominent.

ECG – LV hypertrophy of volume overload type. PR interval may be slightly prolonged. Occasionally bifid P waves from LA hypertrophy.

Echo – Ductus can be imaged running from junction of main and left pulmonary arteries to inner curvature of aorta. Doppler colour flow mapping shows classic diastolic flow from ductus into main pulmonary artery (Figs. 58 and 59).

Cardiac catheterization: Pressure in pulmonary artery somewhat elevated. RA and RV saturations normal, but pulmonary saturation high because oxygenated blood flows from aorta to pulmonary artery (Figs. 60 and 61).

Associated Malformations

- Coarctation of aorta
- Ventricular septal defect
- Aortic stenosis
- Endocardial fibroelastosis
- Atrial septal defect

Complications

- Subacute infective endocarditis.
- Pulmonary hypertension with reversal of shunt.
- Congestive heart failure.

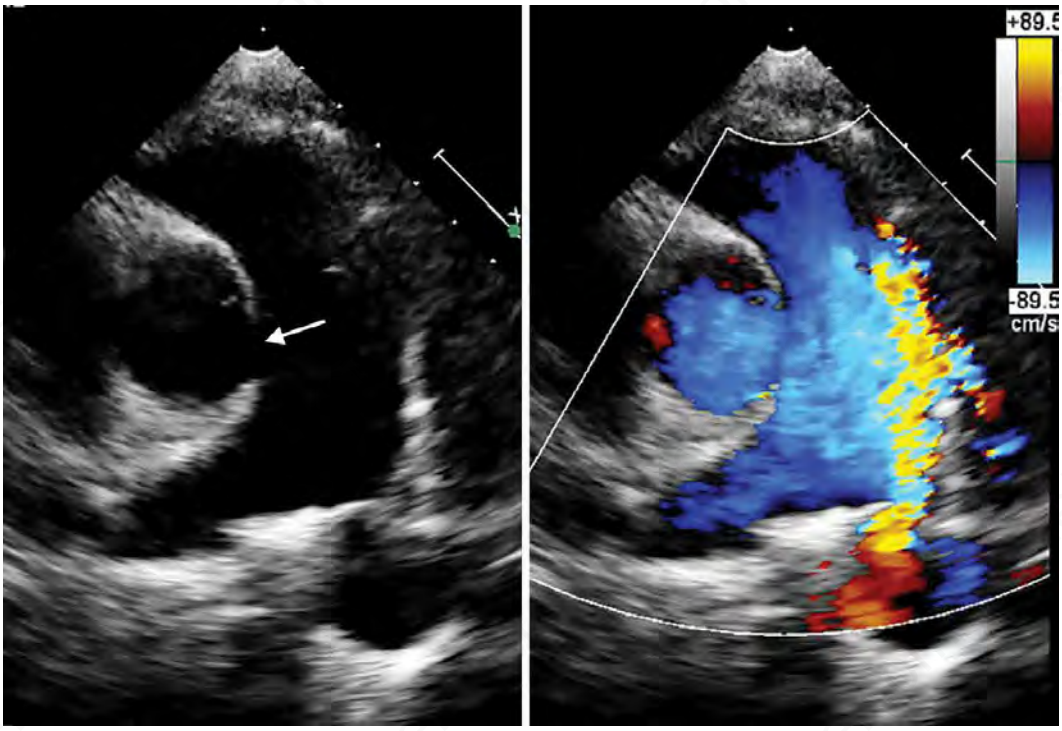


Fig. 59: 2D echo showing patent ductus arteriosus (PDA) (arrow) and flow across it

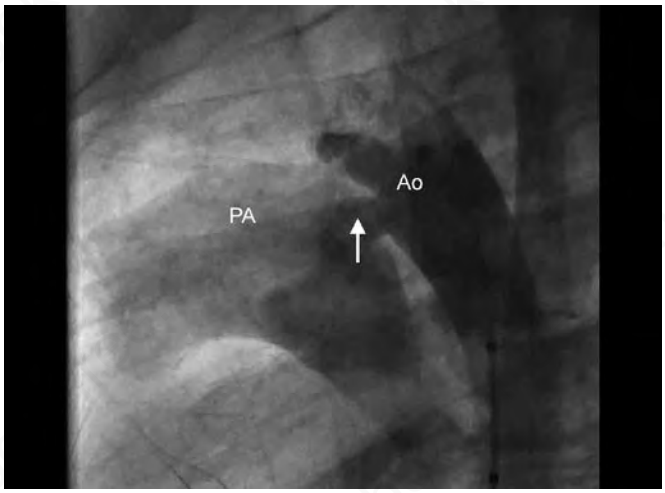


Fig. 60: Large PDA angiography: Amplatzer duct occluder

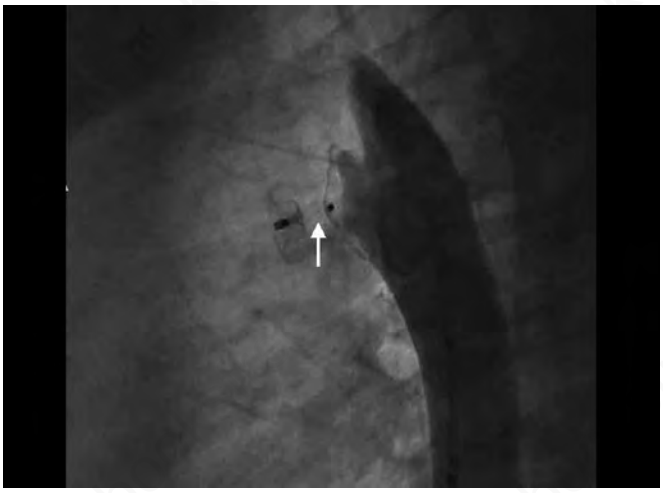


Fig. 61: Large PDA: Amplatzer duct occluder

III. RIGHT-TO-LEFT SHUNT (CYANOTIC)

A. COMMUNICATION BETWEEN THE TWO SIDES OF THE HEART AND GREAT VESSELS

See Tables 39 and 40 for the causes and differential diagnosis of right-to-left shunt.

Eisenmenger's syndrome: Consists of a large communication between the two sides of the heart, pulmonary arterial hypertension at systemic level, and pulmonary obstructive vascular disease that increases pulmonary vascular resistance to a level that reverses the shunt and gives rise to cyanosis.

Table 39: Causes of right-to-left shunt

Common defect:
• Atrial septal defect
• Ventricular septal defect
• Persistent ductus arteriosus (Eisenmenger's disease)
Uncommon defect
• Aortopulmonary septal defect
• Persistent truncus arteriosus
• Transposition of great vessels or
• Corrected transposition with VSD
• Single ventricle
• Single atrium
• Total pulmonary venous drainage into right heart

History

Age at which cyanosis and symptoms appear vary according to the underlying cardiac disorder – exertional fatigue, dyspnoea, syncope, arrhythmias, haemoptysis and anginal pain as the disease progresses.

Signs

1. Central cyanosis. Differential cyanosis in case of PDA.
2. Palpable lift over hypertrophied RV and dilated pulmonary artery.
3. Pulmonary ejection murmur, soft and commonly followed by ejection click.
4. Graham-Steell murmur of pulmonary regurgitation.
5. Pansystolic murmur of tricuspid regurgitation if RV failure.
6. Raised JVP with prominent 'a' wave.
7. Small pulse volume.

Chest radiograph: Gross dilatation of pulmonary arteries with diminished peripheral markings (Fig. 62).

ECG: RV hypertrophy and P pulmonale.

Echo: Imaging of underlying cardiac defect.

Cardiac catheterization: Rise of pulmonary artery and RV pressure to systemic levels. Shunt is predominantly right-to-left. Blood returning from lungs to LA is fully saturated but in LV saturated blood is mixed with unsaturated blood from RV.

MALFORMATION OF RIGHT-SIDED VALVES

TETRALOGY OF FALLOT

Most common cause of congenital cardiac cyanosis in adults.

Table 40: Differential diagnosis of lesions responsible for Eisenmenger's syndrome

	VSD	*PDA*	*ASD*
Symptoms			
Dyspnoea and syncope	Common	Rare	Uncommon
Signs			
Cyanosis, clubbing	Usually from infancy	Differential cyanosis	Usually in adult life
Prominent			
'a' waves	Rare	Very rare	Common
RV lift	+	+	+++
LV lift	+ –	+ –	None
2nd sound	Single	Close split	Wide fixed split
ECG	RVH, LVH	RVH, LVH	RVH, RBBB
	P pulmonale		P pulmonale
Radiology			
RA	–	–	++
Pul. artery	+	+	+++

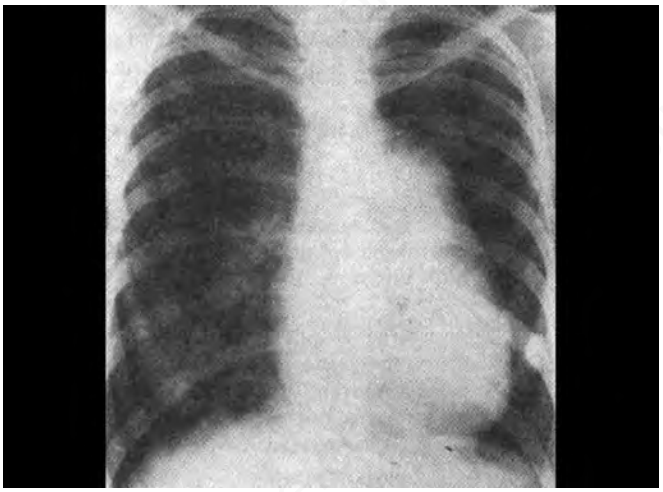


Fig. 62: Eisenmenger ductus arteriosus showing typical dilatation of pulmonary trunk out of proportion to size of hilar arteries

Combination of:

1. High large ventricular septal defect
2. Overriding aorta
3. Right ventricular hypertrophy
4. Pulmonary stenosis

History

Some infants are cyanosed at birth and most by 6 months of age. In some cyanosis may be delayed until adolescence or even adulthood as the right ventricular outflow obstruction becomes progressively severe. Some children become

cyanosed only as they become more active. These children are particularly prone to *hypoxic spells* characterised by crying, rapid deep breathing, initial deepening of cyanosis followed by pallor, limpness or convulsions and loss of consciousness. They are caused by infundibular shut down, preventing blood getting into lungs.

Squatting – Older children may suddenly squat down during exercise. This has the effect of compressing the femoral arteries and thus increasing systemic resistance thus decreasing the right to left shunt. Dyspnoea may also be relieved in this manner by pressure on IVC trapping the venous return to the lungs and reducing the amount of acid metabolites reaching the brain.

Signs

- Clubbing of fingers and toes.
- Ejection systolic murmur maximum in pulmonary area but heard all over the precordium. The murmur may diminish with increasing cyanosis since the pulmonary outflow is very narrow.
- Ejection click due to dilated aortic root may be heard.
- Single 2nd sound. A_2 being audible because the root of aorta is uncovered, P_2 usually absent.
- Continuous murmur if extensive bronchopulmonary anastomosis.
- Absent arm pulses on side of thoracotomy if previous Blalock shunt.

Chest radiograph (Fig. 63):

- RV hypertrophy
- Deep pulmonary bay due to hypoplastic pulmonary artery.

Coeur en sabot (like a wooden shoe) appearance of heart due to lifting of apex of the heart above the diaphragm from RV hypertrophy (seen in 10% of cases).

Pulmonary oligaemia.

Right aortic arch (may be seen).

ECG: RV preponderance. Rarely P pulmonale.

Echo: Visualization of VSD with override of aorta over interventricular septum and visualization of RV outflow tract and infundibular stenosis. Colour flow mapping determines relationship of bidirectional shunting across the VSD and timing of the flows in accordance with the cardiac cycle (Figs. 64 and 65).

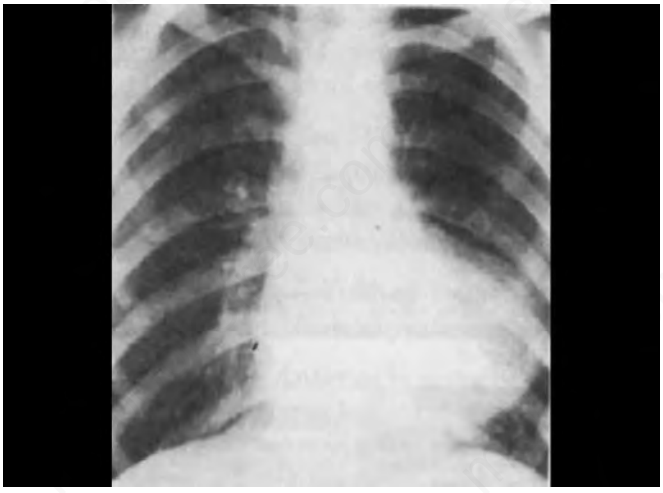


Fig. 63: Fallot's tetralogy. The pulmonary artery is hypoplastic. The lung fields are ischaemic. The apex of the heart is tilted upwards (*coeur en sabot*)

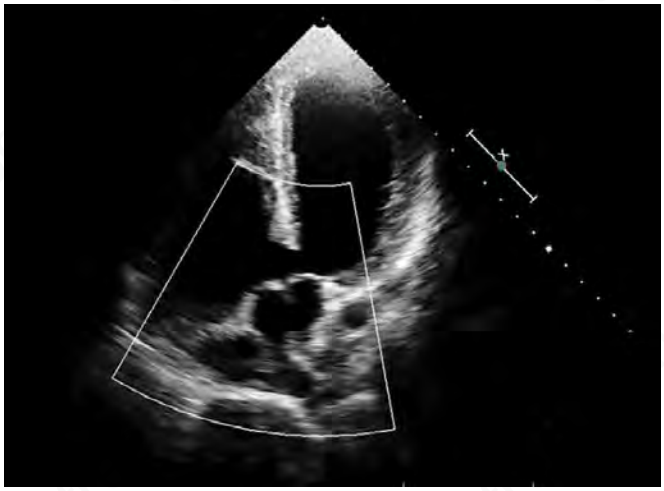


Fig. 64: 2D echo in tetralogy of Fallot (TOF)

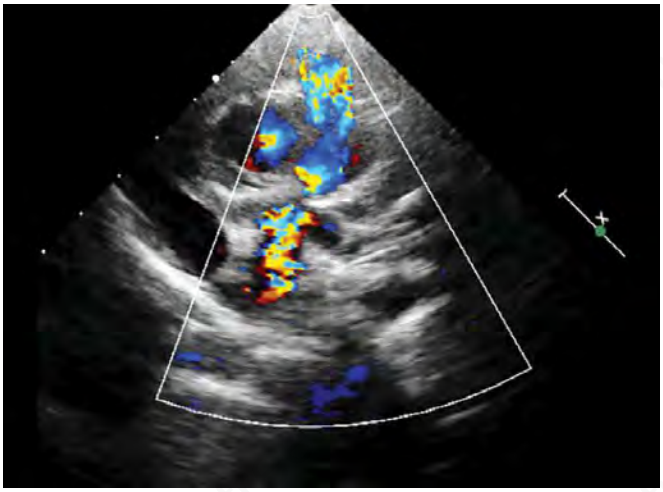


Fig. 65: 2D echo Doppler in tetralogy of Fallot (TOF)

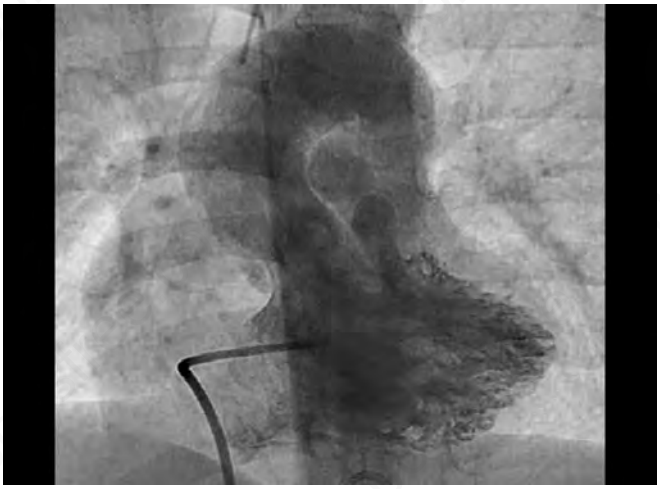


Fig. 66: Angiography in tetralogy of Fallot (TOF)

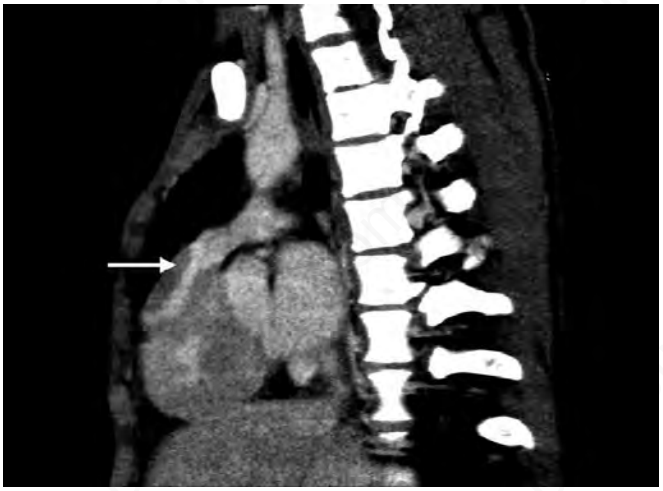


Fig. 67: TOF infundibular pulmonary stenosis

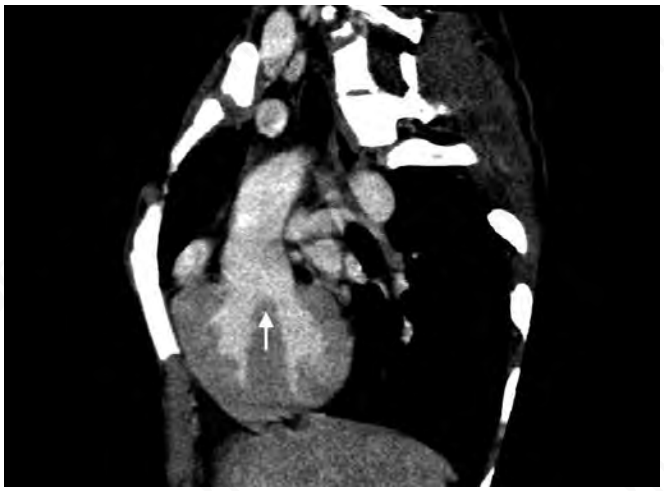


Fig. 68: TOF showing subaortic VSD

Cardiac catheterization: Reduced oxygen saturation in LV. Pressure in pulmonary artery low and in RV greatly elevated (Fig. 66).

MRI (Figs. 67 and 68)

Complications

- Syncope
- Cerebral abscess (paradoxical embolism)
- Stroke due to cerebral thrombosis
- Subacute infective endocarditis
- Sudden death

Table 41 gives differences between Fallot's tetralogy and Eisenmenger's syndrome.

Acyanotic Fallot – The extent of the shunt depends on the degree of obstruction at the outflow tract of RV or at the pulmonary valve. With only slight obstruction there is a bidirectional shunt with no cyanosis. Moon face is common. X-ray shows post-stenotic dilatation of pulmonary artery.

Table 41: Differences between Fallot's tetralogy and Eisenmenger's syndrome

	Fallot's tetralogy	*Eisenmenger's*
Cyanosis	At birth	After first few years
P_2	Soft	Loud
Pul. diastolic murmur	No	May be heard
Radiology	Oligaemic lungs. Good pul. bay	Pul. bay filled due to dilatation of pul. artery

Trilogy of Fallot – PS with reversed interatrial shunt (Table 42).

TRICUSPID ATRESIA

Commonest lesion of clinical importance where central cyanosis is associated with left ventricular hypertrophy. Clubbing is marked.

EBSTEIN'S MALFORMATION OF TRICUSPID VALVE

Blowing systolic murmur secondary to tricuspid regurgitation. Early diastolic murmur over lower precordium is common. ECG – Right atrial enlargement and RBBB. X-ray – Diminished pulmonary vascularity. Enlargement of heart with box-like configuration (Fig. 69).

Table 42: Differences between tetralogy and triology of Fallot's

	Tetralogy of Fallot	*Trilogy of Fallot*
Onset of cyanosis	At birth or within a year	After few years
Squatting	Common	Rare
Facies	Not typical	Often moon face
'a' waves	Small or none	Usually large
RV heave	Absent	Present
Systolic murmur	Rarely loud	Loud with thrill
X-ray chest	Oligaemic lung fields Good pulmonary bay Right-sided aortic arch (25% cases) RV hypertrophy not marked	Oligaemic lung fields but no pulmonary bay No right sided aortic arch RV hypertrophy ++
ECG	No RBBB	RBBB may be present
	Small P pulmonale	Large P pulmonale
Echo	Shunt across VSD	Shunt across ASD
Catheterization	Marked reduction of oxygen saturation in LV No giant 'a' waves Stenosis more often infundibular	Slight to moderate fall in oxygen saturation Giant 'a' waves Stenosis more often valvar

SEVERE PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Systolic thrill with loud harsh ejection systolic murmur in second left interspace with delayed P_2 which is diminished in intensity. ECG – RVH with strain pattern. X-ray – Post-stenotic dilatation of pulmonary artery.

MALFORMATION OF GREAT VESSEL ORIGIN

TRANSPOSITION OF GREAT ARTERIES (TGA)

The aorta arises from RV and pulmonary artery relatively posteriorly from LV. Postnatal survival depends on compensating anomalies (ASD, VSD or PDA) permitting admixture of oxyge-nated blood into systemic circulation. Cyanosis appears early and becomes progressively more severe. Harsh systolic murmur heard at left sternal border. ECG – RVH and strain.

X-ray – Ovoid or egg-shaped cardiac contour (Fig. 70).

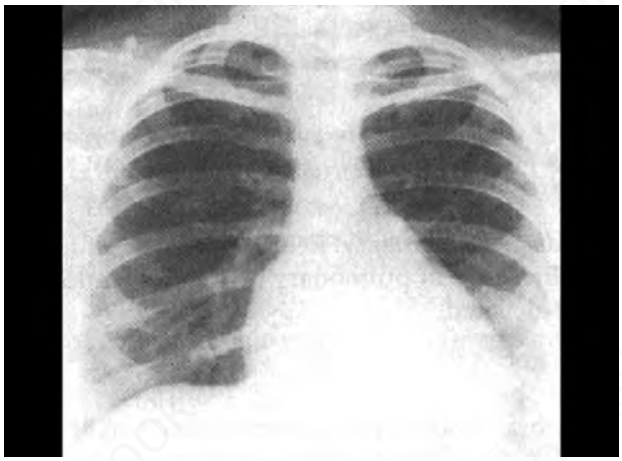


Fig. 69: Ebstein's anomaly. Note the long smooth convexity of the right heart border due to RA enlargement and convex left border with flattened apex due to RV enlargement. Oligaemia

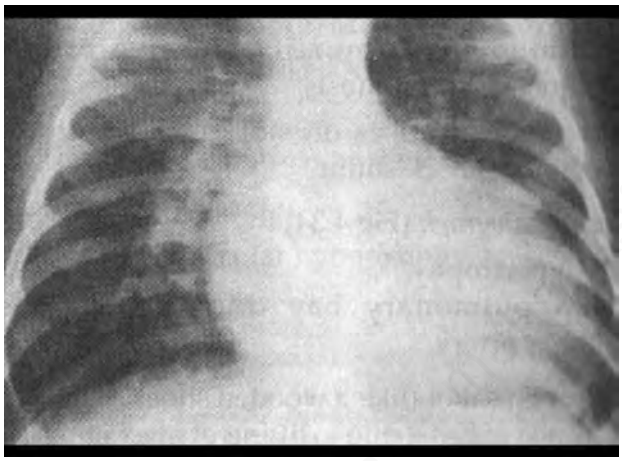


Fig. 70: Complete transposition. Typical appearance of a large 'egg on side' heart, narrow vascular pedicle and plethora

TRUNCUS ARTERIOSUS

Here a single large arterial vessel gives rise to the coronary, pulmonary and aortic arch branches. Systolic thrill and murmur over base of heart. Sometimes early basal diastolic murmur. Single 2nd heart sound. X-ray – Gross biventricular enlargement. Absence of pulmonary arc results in concavity between vascular shadow and ventricle. *ECG*–Biventricular hypertrophy.

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

All blood from the lungs enters RA by one route or another. To enable oxygenated blood to reach systemic circulation, an ASD or patent foramen ovale has to be there.

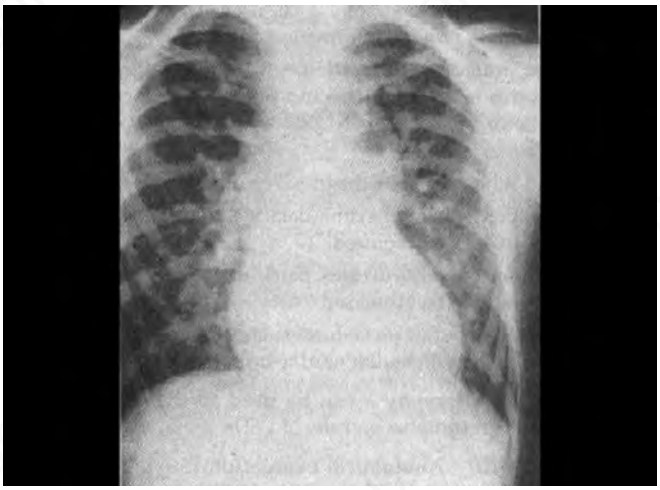


Fig. 71: Typical figure-of-eight (snowman or cottage-loaf) appearance in a case of total anomalous pulmonary venous drainage. In addition there is marked increase in pulmonary vasculature

Signs – resemble those of VSD except – (a) Presence of slight cyanosis. (b) Continuous murmur may be heard in aortic area in 25% of cases.

X-ray – Left SVC with left innominate vein and right SVC produce characteristic cardiac configuration (figure-of-eight, cottage loaf or snowman appearance) (Fig. 71).

Cardiac catheterization – O_2 content of aorta, pulmonary artery and the four cardiac chambers is the same.

INVESTIGATION OF A CASE OF CONGENITAL HEART DISEASE

Clinical:

(a) General

1. *Age* – Cyanosis in infancy 2As, 5Ts
   - Atresia of aorta
   - Atresia of pulmonary artery
   - Transposition of great vessels
   - Tetralogy of fallot
   - Tricuspid atresia
   - Total anomalous pulmonary venous drainage
   - Truncus arteriosus

   If child survives beyond age of 10 years most common lesions are:
   - Atrial septal defect
   - Persistent ductus arteriosus
   - Ventricular septal defect
   - Tetralogy of Fallot
   - Pulmonary stenosis
   - Coarctation of aorta
2. *Rubella syndrome* – may be associated with large PDA or pulmonary valve stenosis.
3. *Clubbing* – of the digits develops in most patients with cyanotic heart disease, it is seldom present before 6 to 9 months of age.
4. *Differential cyanosis* – of upper and lower extremities may occur because of abnormal shunting of blood from pulmonary artery to descending aorta through PDA due to increased pulmonary vascular resistance – (i) Relatively blue toes compared to fingers indicates reversal of flow (right-to-left) through ductus (Eisenmenger PDA or interrupted aortic arch). (ii) Pink toes compared to cyanotic fingers suggests some forms of complex transposition of the great arteries (TGA).
5. *Squatting* – In Fallot's tetralogy.
6. *Stunted growth* – and poor weight gain if marked central cyanosis or severe cardiac failure from a large right to left shunt such as VSD is present.
7. *Face* – (a) Moon facies: High coloured facies as in Cushing's syndrome in PS. (b) Broad, high forehead, low ears, hypertelorism, wide pouting mouth and hypoplastic mandible in supravalvar AS.
8. *Webbing of neck* – Turner syndrome with coarctation. Noonan or Ullrich syndrome with PS.
9. *Chest deformities* – Anterior bowing of chest wall is seen in children with large left to right shunts which cause stiff, non-compliant lungs. Presence of Harrison's sulcus in an older child, who is now well, denotes that a large VSD was present in infancy.
10. *Extremities* – (a) Holt-Oram syndrome: Thumb may resemble a finger (fingerized thumb). Ostium secundum defect is common. (b) Tuft erythema: Red finger tips signify intermittent right to left shunts due to pulmonary hypertension and balanced shunt through ASD. (c) Ellis van Creveld syndrome: Extra finger, often extra toe. (d) Hypoplastic finger nails – ASD, usually ostium primum, or VSD, or single atrium.

(b) Cardiac

1. *Cardiac impulse* – In presence of LVH, the apex beat is localised and thrusting. RVH produces a more diffuse pulsation felt just to the left of sternum. (i) *RVH* – Pulmonary stenosis, ASD. Cyanotic congenital heart disease always causes RVH, the only exception being tricuspid atresia which causes left ventricular hypertrophy. (ii) *LVH* – Coarctation of aorta, PDA, congenital aortic stenosis, persistent truncus arteriosus, tricuspid atresia and single ventricle. (iii) *Biventricular hypertrophy* – may occur with VSD, ostium primum defect,

pulmonary hypertension developing with PDA, persistent truncus.

2. *2nd heart sound* – In ASD widely split and fixed, in Fallot's tetralogy single and clear. Presence of split S_2 excludes diagnosis of truncus arteriosus. S_2 is loud in pulmonary hypertension and soft in pulmonary stenosis.
3. *Ejection clicks* – Aortic ejection clicks are best heard at the apex and occur with bicuspid valve and aortic valve stenosis, but not with subvalvar stenosis. Pulmonary clicks occur with moderate pulmonary valve stenosis but not in severe stenosis, where there is virtually no movement of the deformed valve.
4. *Murmurs* – (a) *Pansystolic* – In VSD along left sternal border in fourth or fifth space. Pansystolic murmur with other signs of ASD suggests septum primum defect. (b) *Early diastolic* – Pulmonary regurgitation secondary to pulmonary hypertension, aortic regurgitation often in association with coarctation of aorta, or bicuspid aortic valve, medionecrosis of aorta and in association with high ventricular septal defect. (d) *Continuous* – PDA, aortopulmonary septal defect as result of congenitally weak sinus of Valsalva, in cases of coronary arteriovenous fistula, or pulmonary AV fistula. Continuous murmur on either side of sternum can also occur in congenital pulmonary atresia. (e) No *murmur* – in a child with central cyanosis and enlarged heart suggests transposition of great vessels.
5. *Pulse* – (a) *Arterial* – Collapsing pulse in PDA, aortopulmonary defect or the rare aortic regurgitation. Femoral pulse delayed and weak or absent in coarctation. An anacrotic, small volume pulse is classically found in AS. (b) *Venous* – Prominent 'a' waves in neck in pulmonary stenosis and pulmonary hypertension.

Investigations

1. ***ECG*** – (a) Right axis deviation and RV enlargement in most congenital cardiac lesions in childhood and adult life. (b) Left axis deviation and LV enlargement in tricuspid atresia. (c) Biventricular hypertrophy – often with large VSD. (d) Arrhythmias – (i) WPW syndrome – especially in Ebstein's anomaly. (ii) AV block – common in corrected transposition of great vessels. May occur with VSD. (iii) RBBB in ASD and other complex defects. (iv) Arrhythmias uncommon in cyanotic CHD except in Ebstein's malformation (atrial tachycardia and atrial flutter).
2. ***Chest radiograph*** – (a) *Plethoric lung fields* – (i) Non-cyanotic – ASD, VSD, PDA. (ii) Cyanotic – Transposition of great vessels, truncus arteriosus, total anomalous pulmonary venous drainage or single atrium, tricuspid atresia with pulmonary stenosis, single ventricle. (b) *Oligaemic lung fields* – PS, Fallot's tetralogy, Ebstein's anomaly. (c) *Conspicuous pulsations of pulmonary arteries* (hilar dance) – ASD, to lesser extent PDA and VSD. (d) *Diminished pulsation of heart* (quiet heart) – Ebstein's anomaly. (e) *Right-sided aortic arch* – common with Fallot's tetralogy, truncus arteriosus. (f) *Dilated main pulmonary artery* in pulmonary valve stenosis or absent in pulmonary atresia. (g) *Typical cardiac silhouettes* – (i) Boot-shaped heart in tetralogy of Fallot. (ii) Egg-on-side appea-rance in TGA. (iii) Cottage loaf – (figure-of-eight) appearance in total anomalous pulmonary venous drainage. (iv) Box-like configuration in Ebstein's anomaly.
3. ***Echocardiography*** – By cross-sectional echocardiography (CSE), the inter-atrial and ventricular septa are easily visualised together with the A-V valves and any defect of clinical significance can almost always be seen, e.g. PDA or coarctation. With the ability of CSE to trace the vena cava, pulmonary veins and great arteries to and from their chambers of origin, complex lesions can be diagnosed. Doppler echocardiography can be used in conjunction with CSE to provide information on blood-flow.
4. ***Cardiac catheterization*** – enables estimation of pressures and saturations and pulmonary vascular resistance.

   Indications:
   (a) Where accurate diagnosis cannot be made.
   (b) Precise hemodynamic data, including response to drugs is required.
   (c) Peripheral structures, particularly in the lungs need to be visualised.
   (d) Therapeutic procedures such as septostomy or balloon dilatation need to be performed.
5. ***Angiography*** – can be used to define for example the number and site of VSDs.
6. ***MRI*** – Anatomical evaluation is typically performed using an ECG-triggered SE sequence with multi-level acquisition. For physiological evaluation, ECG-triggered or ECG-reference forms of cine MRI can be used to evaluate a specific level or to survey cardiac chambers for volumetric analysis.

Management

Of Congenital heart Disease:

A. Of symptoms and/or complications

Congestive heart failure – Diuretics, digoxin, vasodilators. Oxygen, humidification, sedatives. Small frequent feeds.

Cyanosis

Inhibition of ductus closure – Cyanosis in early neonatal period is characteristic of transposition of vessels and of defects associated with reduced pulmonary blood flow. Such infants have a ductus arteriosus dependent pulmonary blood flow and deteriorate as the ductus constricts after birth. Ductus closure can be inhibited by IV infusion of Prostaglandin E1 or E2 at a rate of 0.005–0.01 µg/min. If cyanosis is severe rate can be increased initially to 0.05–0.1 µg/kg/min for 15–30 min. to achieve effective dilatation of an already constricted ductus. Side-effects—Pyrexia, hypotension and apnoeic attacks which may require intubation and positive pressure ventilation. If cyanosis not severe – Oral prostaglandin E2 62.5–125 µg/hour may be effective.

Acidosis – may develop in a severely hypoxic infant and may need treatment with sodium bicarbonate.

Polycythemia – can be progressive in presence of severe cyanosis and may predispose to cerebral infarction especially if the child gets dehydrated from vomiting or diarrhoea. In any cyanosed patient, Hb and PCV should be monitored at regular intervals. If PVC rises more than 65%, venesection (not more than 10 mL/kg at a time) or urgent surgery may be necessary. Oral iron if evidence of anaemia.

Hypoxic attacks – The child must be picked up and soothed. If not effective in reducing distress and agitation, Inj. morphine 0.2 mg/kg IM. Nursing the child in knee-chest position may help. Oxygen. To reduce frequency and severity of hypoxic attacks – Propranolol 0.5–12 mg/kg q8h by mouth as temporary measure till surgery.

Prophylaxis of infective endocarditis – Advice on dental hygiene and regular dental checks. Antibiotic cover for major dental treatment.

B. Treatment of Underlying Defect

Defects not associated with shunts –

Coarctation of aorta – In infants early onset of symptoms is related to poor perfusion of lower systemic segment after closure of ductus. Re-opening the ductus with Prostaglandin infusion may lead to improvement. Additional support with catecholamines, e.g. Dopamine 5 µg/kg/min may be necessary.

Surgery is indicated if upper segment hypertension or significant associated intracardiac defects. Resection and end-to-end anastomosis, or subclavian flap aortoplasty.

Aortic stenosis – Surgical valvotomy, or balloon valvuloplasty. If re-stenosis occurs, valve replacement may be necessary.

Pulmonary stenosis–If moderate or severe obstruction, balloon valvuloplasty. Surgical valvotomy rarely necessary.

Defects with left-to-right shunts –

VSD

- *Large VSD* – Direct repair of VSD because of increasing pulmonary hypertension.
- *Moderate VSD* – Catheter studies at 1 year of age.

Operative correction or transcatheter closure is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio > 1.5:1, in the absence of severe pulmonary vascular resistance (pulmonary arterial resistance is less than two-third of systemic arterial resistance).

Mild defect – Follow-up with echo and catheter studies.

Contraindications to surgery:

(1) $\frac{PBF}{SBF} > 2$

(2) Greatly increased pulmonary resistance. Technique – (a) Through RV to avoid damage to AV bundle. ECG is done before closing to reverse any block due to surgery. (b) Through LV if multiple small openings. (c)Through RA into RV (incision on atrial appendage).

PDA – *Premature infants* – Symptoms should be treated with fluid restriction and diuretics. If no improvement – Indomethacin 0.2 mg/kg orally, rectally or IV. If ineffective surgical ligation.

Children – Even a small PDA carries risk of infective endocarditis and surgical ligation or transcatheter occlusion with detachable coils should be done as soon as diagnosis is made.

ASD – Children with ASD are often asymptomatic but it may lead to atrial fibrillation and congestive failure in adult life. Repair is therefore advisable during childhood.

DEFECTS ASSOCIATED WITH RIGHT-TO-LEFT SHUNTS

Tetralogy of Fallot

Management depends on nature and extent of obstruction to pulmonary blood flow. If marked hypoplasia of pulmonary artery – Palliation with one or more systemic-to-pulmonary shunt procedure, e.g. subclavian and pulmonary artery (Blalock-Taussig shunt).

If severe hypoxia and cyanosis are present, early surgery is necessary.

Ultimate surgical repair involves VSD closure (with a prosthetic patch) and relief of outflow tract obstruction often with placement of a transvascular gusset. In favourable cases total correction has a mortality of less than 5%.

TPGA

Initial treatment of correction of acidosis and if necessary IV prostaglandin. Corrective surgery can be carried out in neonatal period by re-implanting the aorta, pulmonary artery and coronary arteries at their normal site (arterial switch procedure). Alternately, definite surgery can be postponed in infants with intact ventricular septum and low pulmonary pressure to first year of life. Surgery then consists of atrial redirection procedure in which pulmonary veins are connected to RA and SVC and IVC are drained into left atrium.

TAPVC – Reconnection of pulmonary veins to LA and obliterating abnormal connections to systemic venous system or RA.

Tricuspid atresia – Initial– Systemic-to-pulmonary shunt operation. Definitive surgery at age of 2–4 – Returning blood from systemic circulation (via SVC and IVC) is directed into pulmonary circulation without traversing the right side of the heart except a portion of RA which is connected to pulmonary arteries directly (Fontan procedure).

6. VALVULAR HEART DISEASE

MITRAL VALVE DISEASE
MITRAL STENOSIS

Causes

See Table 43 for the causes of mitral stenosis. Rheumatic fever is the most common etiology in India. As a result of rheumatic endocarditis chordal fusion, leaflet thickening or commissural fusion develops giving rise to funnel-shaped deformity of the valve with button hole orifice.

Table 43: Causes of mitral stenosis

• Rheumatic fever
• Congenital (parachute valve or commissural fusion).
• Associated with ASD (Lutembacher's syndrome).
• Hurler's syndrome (Gargoylism).
• Endomyocardial fibrosis (regurgitation more common).
• Calcified mitral annulus in elderly.
• Functional due to partial obstruction of valve orifice:
– Left atrial tumour usually myxoma.
– Left atrial ball valve thrombus.
– Cor triatriatum.
– HOCM with obstruction to left ventricular inflow.
• SLE, RA
• Juvenile MS (Table 44)

Symptoms

1. **No symptoms** – Discovered during pregnancy, routine physical examination or supervening infective endocarditis. There are no symptoms until the valve area is reduced to 1.5 cm^2.
2. **Respiratory symptoms**
   (a) *Dyspnoea* – due to pulmonary hypertension. As the pulmonary artery pressure rises, exercise tolerance decreases.
   Grades of dyspnoea:
   - Grade 1: No breathlessness
   - Grade 2: Breathlessness on severe exertion
   - Grade 3: Breathlessness on mild exertion
   - Grade 4: Breathlessness at rest.

   Mechanism of pulmonary hypertension:
   - Backward extension of raised LA pressure.
   - Reactive arteriolar constriction.
   - Embolic obstruction to pulmonary vasculature.
   - Hypoxic vasoconstriction when CHF develops.
   - Interstitial oedema in walls of small pulmonary vessels

   (b) *Pulmonary edema* – Usually precipitated by severe exertion, pregnancy, onset of atrial fibrillation, respiratory infection and occasionally by anesthesia.
   (c) *Haemoptysis* may be initial symptom or occur late (Table 45).

Table 44: Salient features of juvenile MS

1.	Occurrence in tropical areas.
2.	Incidence early in life (<18 yrs).
3.	AF rare
4.	No valve calcification
5.	Pin-point stenosis
6.	Rapidly progressive with development of pulmonary hypertension and CHF
7.	Urgent surgery necessary

Table 45: Mechanisms of hemoptysis in mitral stenosis

• Sudden large haemorrhage from pulmonary veins (pulmonary apoplexy)
• Blood-stained sputum due to pulmonary venous congestion
• Blood-tinged sputum during an attack of bronchitis
• Pink frothy sputum associated with acute pulmonary oedema
• Following pulmonary infarction
• Pulmonary haemosiderosis
• Rupture of bronchial submucosal varices
• Anticoagulant overdosage

Protective mechanisms against development of PND in long-standing MS – (a) Pulmonary hypertension. (b) Capillary-alveolar-interstitial barrier. (c) Presence of broncho-pulmonary venous shunts.

(d) *Recurrent attacks of bronchitis* – may occur.

3. *Palpitation* – may occur with regular or irregular rhythm.
4. *Angina pectoris* – in presence of tight MS attributed to dilatation of pulmonary artery, pulmonary vascular obstruction with right ventricular ischaemia, left ventricular ischaemia from poor cardiac output or coronary embolization.
5. *Fatigue* – from low cardiac output.
6. *Embolism* – Systemic or pulmonary.
7. *Cyanosis* – usually peripheral due to low cardiac output. Central cyanosis may result from pulmonary congestion.
8. *Symptoms due* to *pressure of dilated left atrium* –
   (a) Hoarseness of voice – may progress to aphonia, due to compression of left recurrent laryngeal nerve (Ortner's syndrome).
   (b) Dysphagia – from pressure on oesophagus.
   (c) Collapse of lung – rare, due to compression of left main bronchus by a giant left atrium.
9. *Infective endocarditis* – rare with pure MS.
10. *Massive thrombus in left atrium* – is usually associated with atrial fibrillation, may cause sudden death.

Signs

Inspection

1. *Mitral facies* (Malar flush) – Cyanotic hue over cheek bones due to low cardiac output (if severe stenosis).
2. Giant 'a' waves in jugular venous pulse if pulmonary hypertension.

Palpation

1. Apex impulse normal, or brief tapping corresponding to the tap of the mitral 1st heart sound (closing snap).
2. Left parasternal heave due to RV hypertrophy.
3. Palpable P_2 in second left space.
4. Presystolic and mid-diastolic thrill may be felt at the apex.

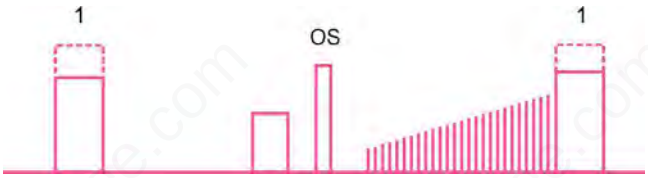


Fig. 72: Mid- and late-diastolic (presystolic) murmur of mitral stenosis with accentuated first heart sound at the apex and opening snap

Auscultation

1. *Loud 1st heart sound* – This results from two factors – (a) The high left atrial pressure keeps the mitral cusps open until the very end of diastole. (b) Fibrotic changes in the mitral valve leaflets alter them in such a way that they tense more abruptly with ventricular contraction. If the valve is heavily calcified the first sound will not be accentuated.

   Causes of muffled S_1 – (a) Heavily calcified valve. (b) Associated prominent MR or severe AR. (c) Prolonged PR interval (active rheumatic carditis or digitalis overdosage). (d) Gross RVH with RV forming the apex. (e) Acute MI. (f) Left atrial failure.
2. *Presystolic murmur* – often a relatively early sign, usually disappears with onset of atrial fibrillation or LV failure or presence of large LA thrombus. The murmur of mitral stenosis is localised to the apex, best heard on expiration, after exercise and with the patient turned on to the left side.

   Causes of softening of MS murmur – (a) Mild MS. (b) Large RV pushing LV posteriorly away from anterior chest wall. (c) Associated ASD.
3. *Mitral opening snap* – occurs as the disease valve is snapped open forcibly by high pressure in LA. Heard best at apex shortly after 2nd sound. Shorter the interval between the sound and opening snap (2-OS interval) tighter the stenosis (Fig. 72). At times OS may be absent (Table 46).
4. *Apical mid-diastolic murmur* – occurs after the opening snap and increases in length as the stenosis becomes more severe. It eventually merges with the presystolic murmur if LV filling is severe enough for there to be turbulent filling across the valve for the whole of diastole.

Table 46: Causes of absent OS

• Mild or early stenosis.
• Long duration of preceding diastole allowing high LA pressure to fall.
• Associated AR, the regurgitant stream slowing rate of movement of the valve displacement to LV.
• Markedly calcified or fibrosed valve.
• Associated MR of moderate degree.
• Extremely low flow due to very severe stenosis, secondary pulmonary hypertension, concomitant aortic or pulmonary valve disease or myocardial dysfunction.
• Fusion or matting of chordae tendinae and papillary muscles of left ventricle.
• Large RV that pushes LV away from chest wall.

5. *Early diastolic murmur* – in pulmonary area caused by pulmonary regurgitation from stretching of pulmonary artery by pulmonary hypertension.

Degree of stenosis

1. *Symptoms:* The normal mitral valve is 4–6 cm^2 in area. Symptoms begin to develop when valve stenoses to 1.5 cm^2 and usually become severe once the area is < 1.5 cm^2.
2. *Signs:*
   - A_2OS interval shortens
   - Marked RV heave
   - Very loud apical S_1 (unless valve calcified or ankylosed).
   - Loud P_2
   - Long diastolic murmur
   - Graham-Steell murmur of pulmonary regurgitation
   - Low pulse volume
3. *Doppler measurement* – of the flow across the valve. Severe lesion if measured orifice area (cm^2) < 1.0.

Investigations

1. ***Chest radiograph*** (Fig. 73)
   (a) *Cardiac silhouette*
   - Heart is not usually enlarged.
   - Left atrial enlargement causes – (i) Double contour of right heart border. (ii) Elevation of left main bronchus. (iii) Splaying of carinal angle. (iv) Posterior displacement of barium-filled oesophagus.
   - Enlargement of main pulmonary artery if pulmonary hypertension.
   - Calcification in valve, or left atrium if thrombus in left atrial wall.
   - Enlargement of left atrial appendage produces localised bulge just below pulmonary artery thus straightening the left heart border.

   (b) *Lung fields* – With increasing left atrial pressure the changes seen in increasing order of severity are –
   - Dilatation of pulmonary veins of upper lobes.
   - Oedema of interlobular septa (Kerley B lines) with interstitial oedema and small parietal pleural effusions.
   - Alveolar oedema, perihilar haze and effusion.
   - Prominence of upper lobe veins seen as thick branching opacities from pedicle of the heart due to increased left atrial end diastolic pressure (Moustache or Antler sign).
   - As pulmonary hypertension develops, the pulmonary venous congestion becomes less marked and is replaced by proximal pulmonary artery enlargement. With long-standing elevation of left atrial pressure, miliary mottling may appear from pulmonary haemosiderosis.
2. ***ECG*** – (i) Prominent, wide and notched P waves (M shaped) in leads I and II, with mainly upright P in V_1 (P mitrale). (ii) Right ventricular preponderance (Fig. 74).
3. ***Echo*** – (a) Reduced closure rate of mitral anterior cusp. (Reduced EF slope). (b) The posterior leaflet is pulled in the same direction as the anterior leaflet since the chordae are fused. (c) A calcified fibrotic valve produces multiple echoes with insignificant diastolic movement (Figs. 75 to 78).

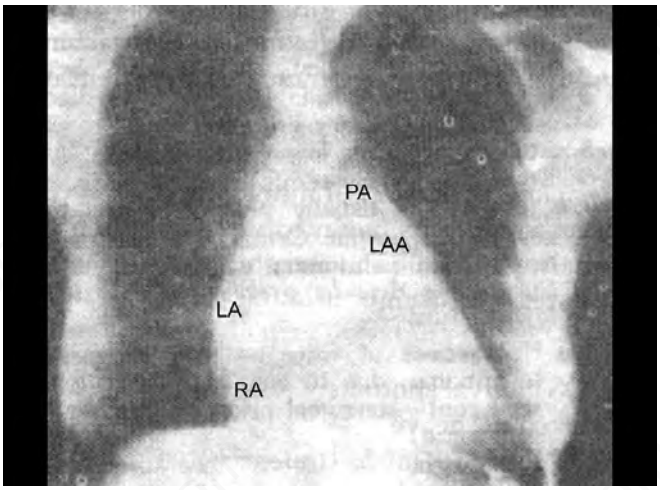


Fig. 73: Mitral stenosis. An enlarged left atrial appendage (LAA) protrudes on the left border of the heart, between the pulmonary artery and the left ventricle. [A double shadow at the right heart border is due to left atrial (LA) enlargement]. Left heart border straight due to enlargement of pulmonary bay and LA enlargement (mitralisation)

Differential Diagnosis

For the causes of diastolic apical murmur (Refer).

Cor triatriatum: Clinically, the symptoms may be identical with MS including paroxysmal nocturnal dyspnoea and haemoptysis and at times a presystolic murmur.

Management

I. ***Mitral valvotomy***

Indications of mitral valvotomy are given in Table 47 (Fig. 79).

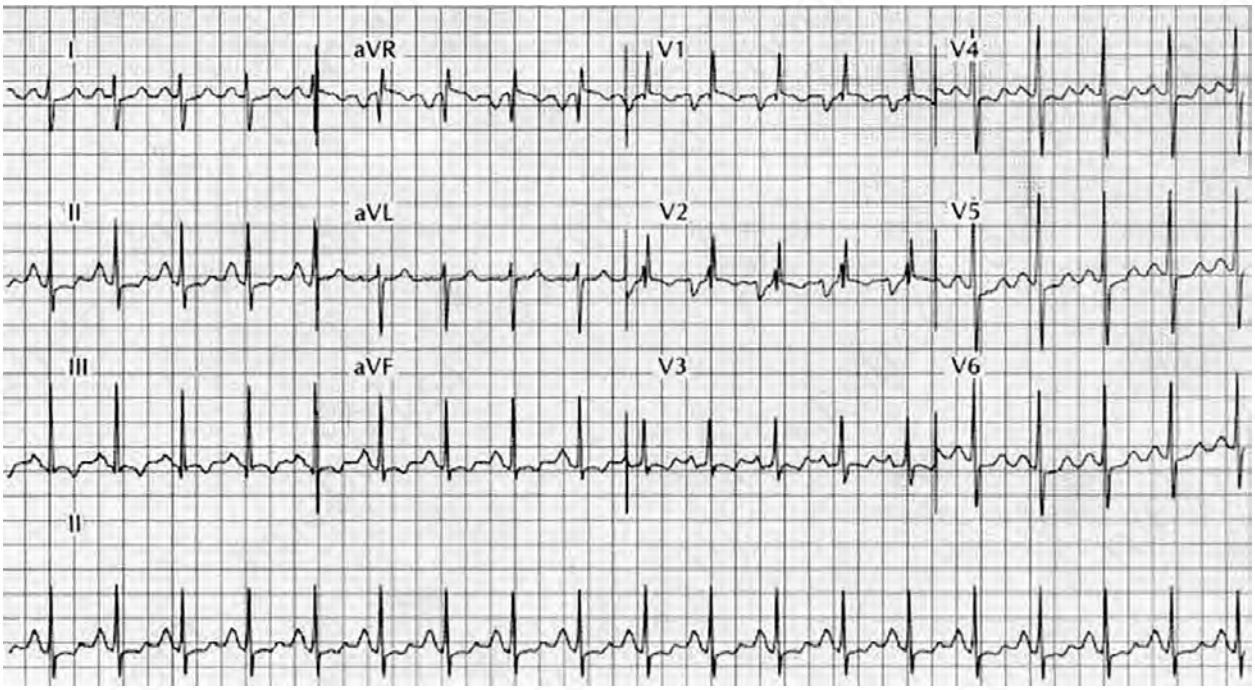


Fig. 74: ECG in severe mitral stenosis

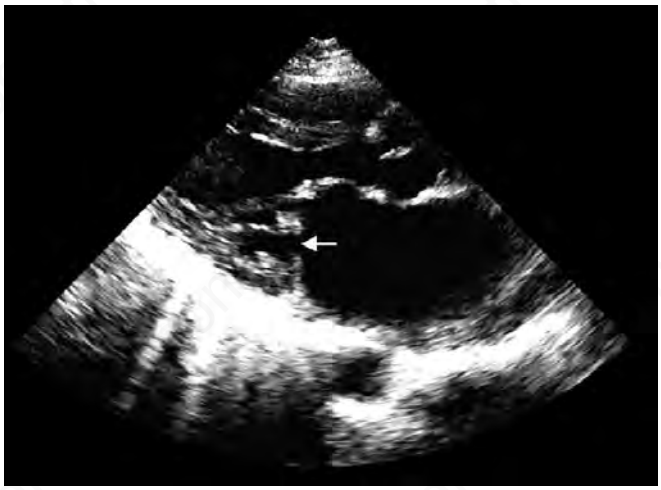


Fig. 75: D2 echo in mitral stenosis

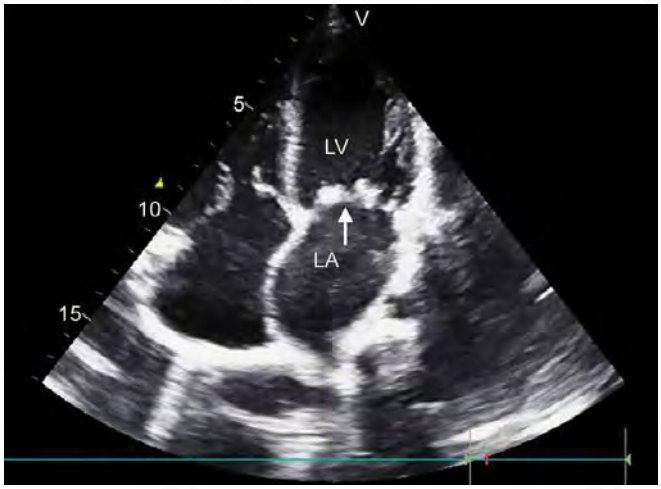


Fig. 76: Apical four chambered view showing thickened mitral valve with restricted opening in mitral stenosis

II. ***Medical***

1. *Prevention of recurrence of rheumatic fever* – especially in younger patients. Prophylactic oral penicillin V 250 mg. b.d. or in patients who are unreliable in taking oral therapy – Benzathine penicillin G 1.2 million units IM once a month. If patient is allergic to penicillin, erythromycin 250 mg. daily by mouth.
2. *Prevention of infective endocarditis* – (Refer).
3. *Prevention of too rapid ventricular rate* – Digitalis if – (i) Atrial fibrillation. (ii) Older patients who are still in sinus rhythm to prevent paroxysmal atrial fibrillation.
4. *Prevention of pulmonary venous congestion and pulmonary oedema* – Diuretics. Surgery in patients with severe stenosis.
5. *Prevention of embolism* – Long-term anticoagulant therapy (Table 48).

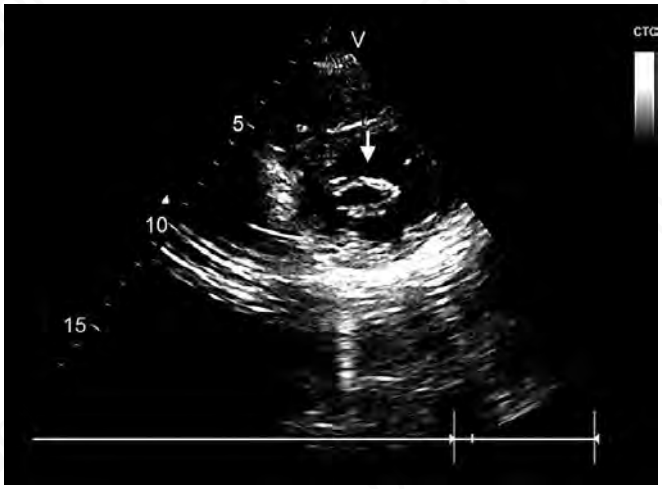


Fig. 77: Parasternal short axis view in MS showing the typical 'fish mouth' appearance of the narrowed mitral valve orifice in diastole

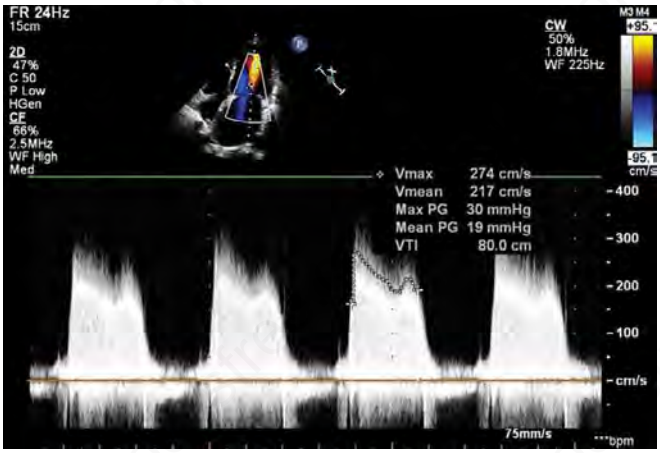


Fig. 78: Echo Doppler in mitral stenosis

Table 47: Indications of mitral valvotomy
a. Significant symptoms limiting activity
b. Uncontrolled atrial fibrillation causing marked deterioration
c. Episode of pulmonary oedema without obvious precipitating cause
d. Following embolization
e. Pulmonary oedema during pregnancy

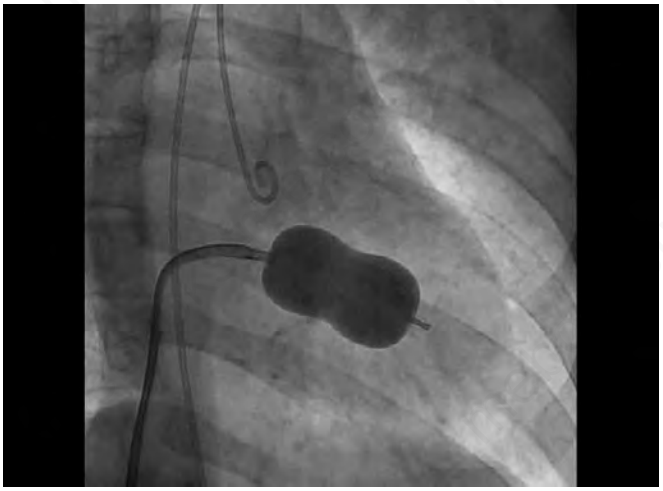


Fig. 79: Balloon mitral valvotomy (BMV)

Table 48: Indications of anticoagulant therapy in mitral stenosis
Moderate to severe stenosis
Enlarged left atrium
Atrial fibrillation
Sinus rhythm with recurrent palpitations
Any symptoms suggestive of arterial embolism

MITRAL REGURGITATION

Causes

See Table 49 for causes of mitral regurgitation.

Symptoms

1. No symptoms with mild degree of MR.
2. Symptoms due to pulmonary congestion – effort dyspnoea progressing to orthopnoea and paroxysmal cardiac dyspnoea.
3. Symptoms due to congestive heart failure.
4. Dramatic onset of symptoms with at times frank pulmonary oedema with chordal rupture or sudden papillary muscle dysfunction.

Signs

- *Pansystolic murmur* – High pitched, blowing, starts immediately after the first sound, and continues just beyond aortic valve closure because LV pressure is still higher than LA pressure at this time. Maximal at apex, radiating to axilla and left posterior or interscapular area of chest in the direction of the jet. As a rule more severe the degree of insufficiency louder the murmur. When regurgitation occurs principally through the posterior leaflet, the murmur may be referred to the base of the heart and may be audible even in the neck vessels (Fig. 80).

Table 49: Causes of mitral regurgitation

A.	**Organic MR**
	Common:
	• Rheumatic fever.
	• Infective endocarditis
	• Papillary muscle dysfunction or rupture (subvalvar MR) usually due to myocardial infarction.
	Uncommon:
	• Cardiomyopathy - Dilated, hypertrophic
	• Congenital – Associated with ostium primum defect.
	• Libman-Sacks syndrome in SLE.
	• Endomyocardial fibrosis.
	• Surgical trauma to stenotic mitral valve.
	• Prosthetic valve malfunction
	Rare:
	• Mitral valve prolapse.
	• Floppy valve ± chordal rupture.
	• Calcified valve ring (usually mild and in very elderly).
	• Collagen abnormalities, e.g. Marfan's, Ehlers-Danlos syndrome, ankylosing spondylitis.
	• Kawasaki disease
B.	**Functional MR**
	• Acute rheumatic and viral myocarditis.
	• Ischaemic heart disease.
	• Hypertension.
	• Aortic valve disease.
	• Congestive cardiomyopathy.

- *Soft first heart sound.*
- *Loud third heart sound* – Usually audible at apex in severe regurgitation, caused by rapid filling of LV.
- *Mid-diastolic short apical murmur* – may be heard in some cases with very large flows across the mitral valve.
- *Wide expiratory splitting of second sound* – because of short ejection time and early closure of aortic valve in severe MR.
- *Opening snap* – if severe MR or MR due to endomyocardial fibrosis.

Signs of Severe of MR

- Loud pansystolic murmur
- Systolic apical thrill
- Hyperdynamic LV impulse
- Ventricular gallop
- Mitral diastolic flow murmur

Fig. 80: Pansystolic murmur of mitral regurgitation beginning with the first sound and ending with or enveloping aortic valve closure of second heart sound. A loud third heart sound of increased ventricular filling may be heard

- Opening snap
- Left parasternal heave due to systolic expansion of LA which pushes RV forward.

Subvalvular Regurgitation

(a) *With papillary muscle dysfunction and chordal rupture*– the systolic murmur is often short and confined to mid or late systole and resembles an ejection murmur.

(b) *With posterior chordal rupture* – the posterior mitral leaflet balloons into the left atrium during ventricular systole, and the regurgitant jet is anteriorly directed. The murmur is therefore prominent in the aortic area, simulating aortic stenosis.

Acute MR – Murmur loud, apical and pansystolic, and often accentuated in late systole. Rapid, sharp, small volume pulse and pulmonary oedema.

Investigations

X-ray – In severe cases, LA (may be aneurysmal) and LV enlargement, later RV enlargement. If LA is disproportionately small in comparison with the large size of LV or degree of mitral regurgitation, papillary muscle dysfunction or ruptured chordae likely. With high LA pressure Kerley B lines. Small heart or slight cardiac enlargement (Fig. 81) and pulmonary oedema in acute MR (Fig. 82).

ECG – P mitral. In severe cases LVH**.**

Echocardiography – Rupture of chordae tendinae of mitral valve as a cause of MR may be suspected from an abnormally great separation of anterior and posterior cusp echoes, and from an abnormally large range of movement of anterior leaflet. The degree of LV dilatation reflects the severity of regurgitation (Figs. 83 and 84).

Cardiac catheterization – Adds little information about the valve lesion but the coronary anatomy helps in determining the aetiology of MR and planning treatment.

Complications – Same as MS except incidence of AF and embolism is less, and that of IE greater.

Differential Diagnosis – See D.D. of systolic murmurs.

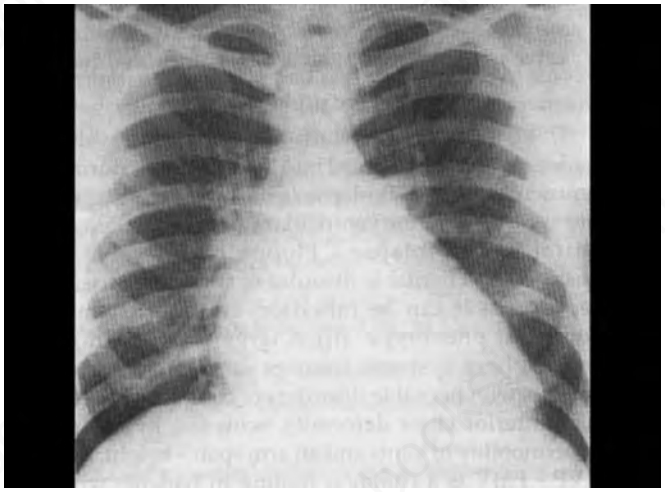


Fig. 81: Radiological appearances in case of severe mitral regurgitation showing considerable dilatation of the left atrium and left ventricle and marked pulmonary venous congestion

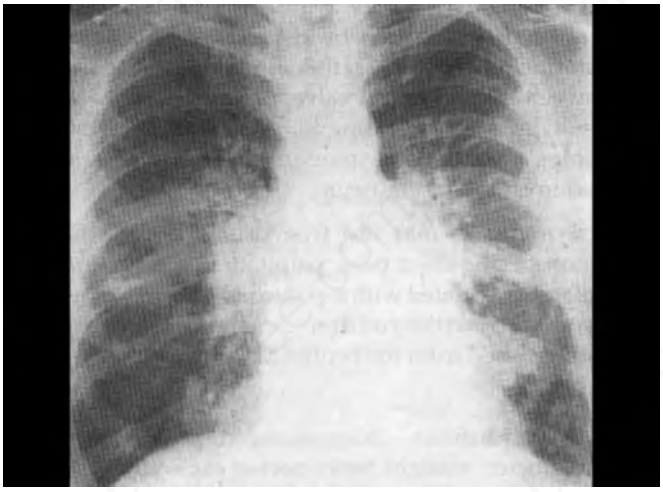


Fig. 82: Acute MR. Slight cardiac enlargement, pulmonary oedema (Bat's wing appearance)

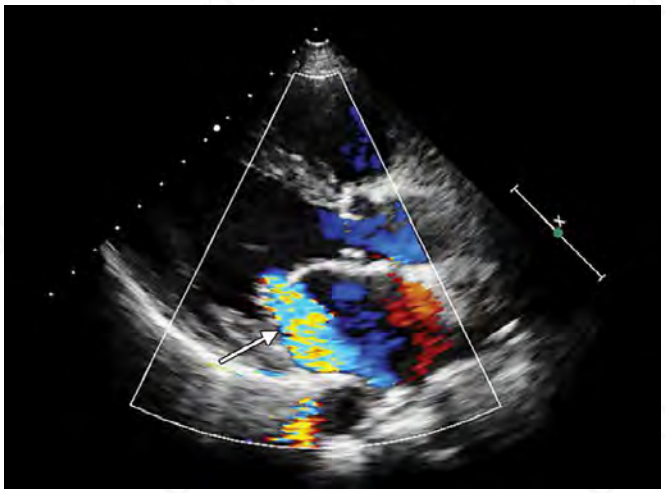


Fig. 83: Echo Doppler showing regurgitant flow in mitral regurgitation

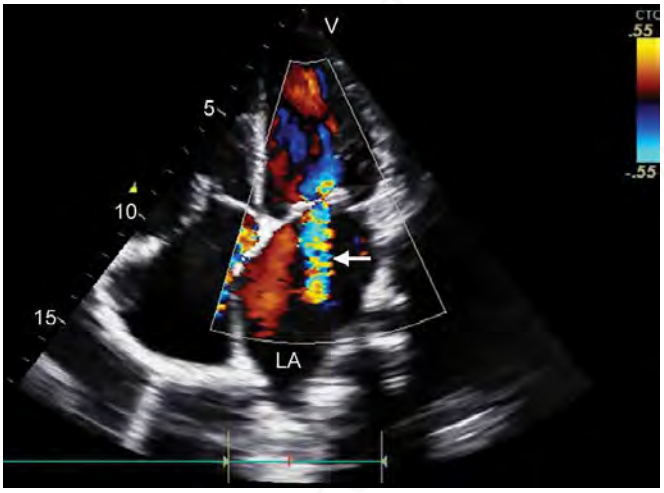


Fig. 84: Apical 4-chamber view showing mitral regurgitant jet (arrow) travelling from LV to LA

Management

- *Medical* – As for mitral stenosis.
- *Surgical* – In severe cases replacement of mitral valve with prosthetic valve, or repair procedure.

MITRAL VALVE PROLAPSE (MVP)

This is a condition in which one or both mitral valve leaflets prolapse backward into the left atrium during ventri-cular systole. Prolapse is most marked during late systole when the ventricular cavity is smallest.

Mitral valve prolapse – Floppy mitral valve is classified as a heritable disorder of connective tissue because (i) It can be inherited as an autosomal dominant phenotype. (ii) A large proportion of patients have systemic features similar to those of patients with heritable disorders of connective tissue (e.g. anterior chest deformity, scoliosis, kyphosis, hypermobility of joints and an arm span > height. (iii) MVP - FMV is a common finding in patients with recognized heritable disorders of connective tissue (e.g. Marfan syndrome, Ehlers-Danlos syndrome, and adult polycystic kidney disease.

Pathogenesis

MVP is a multifactorial valvular abnormality that can be caused by histological abnormalities of valvular tissue, geometric disparities between LV and mitral valve, or various connective tissue disorders including Marfan syndrome, Ehlers Danlos syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum.

Symptoms may vary from usually none to those of nonspecific chest pain, palpitation and tiredness. Prolapse associated with myocardial ischaemia may be associated with sudden death and must be distinguished from the benign MVP syndrome.

Signs

1. Typical habitus – Narrow anteroposterior chest diameter, straight back, pectus excavatum, long extremities and hyper-reflex joints.
2. Apical mid-systolic click (sometimes multiple) and/or
3. Late systolic murmur, loudest at the apex. Manoeuvres that reduce LV volume (standing, sublingual nitroglycerine) make the valve prolapse earlier and make the murmur and click appear earlier in systole, while those which increase LV volume (lying, squatting) make both occur late in systole.

Complications

See Table 50 for the complications of MVP.

Clinical associations of MVP: (a) Marfan's or Ehlers-Danlos syndrome. (b) ASD (secundum defect). (c) Heart muscle disease – HOCM, ischaemic or rheumatic heart disease. (d) Wolff-Parkinson-White syndrome. (e) Poly-arteritis nodosa. (f) Adult polycystic disease. (g) Postvalvotomy.

The term 'Mitral valve prolapse syndrome' is used to differentiate prolapse associated with non-specific symptoms (chest pain, palpitations, pre-syncope or syncope, effort syndrome).

Investigations

- *ECG:* It may be normal or show ST and T wave changes in leads III, aVF.
- *Echo:* Single or bileaflet prolapse at least 2 mm beyond the long axis annulus, with or without leaflet thickening (Figs. 85 and 86).
- *Cardiac catheterization:* Left ventriculography often demonstrates prolapse of mitral leaflets. Degree of MR can be estimated and in patients with chest pain, coronary artery anatomy can be defined.

Table 50: Complications of MVP

• Cardiac arrhythmias (usually ventricular ectopics).
• Infective endocarditis.
• Systemic emboli (generally manifest as TIAs).
• Ruptured chordae tendinae.
• Severe MR.
• Sudden death.

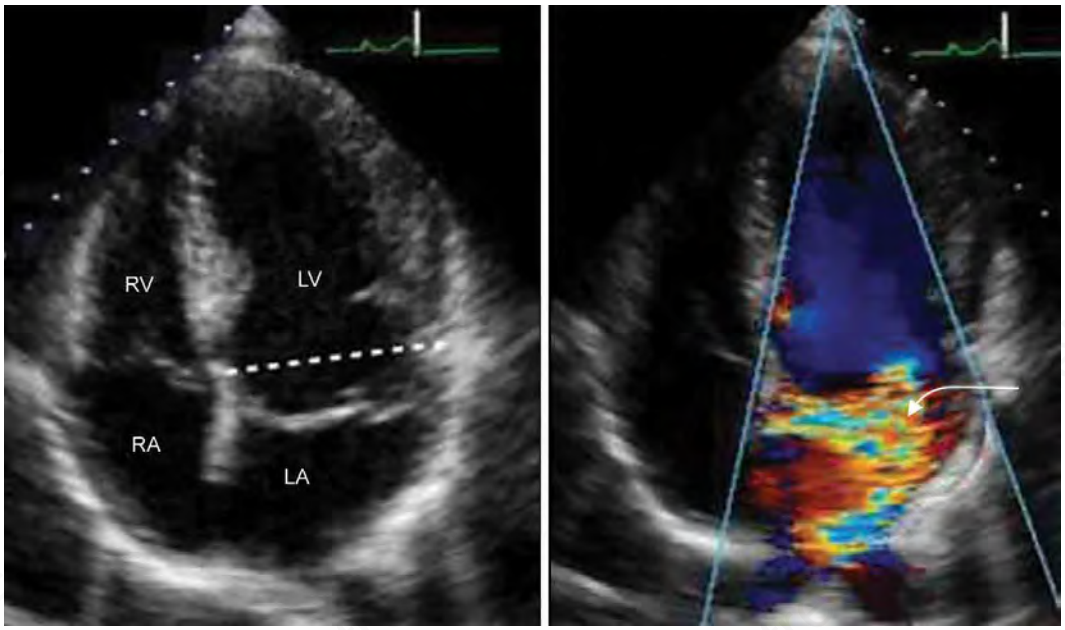


Fig. 85: 2D echo and Doppler in mitral valve prolapse (MVP)

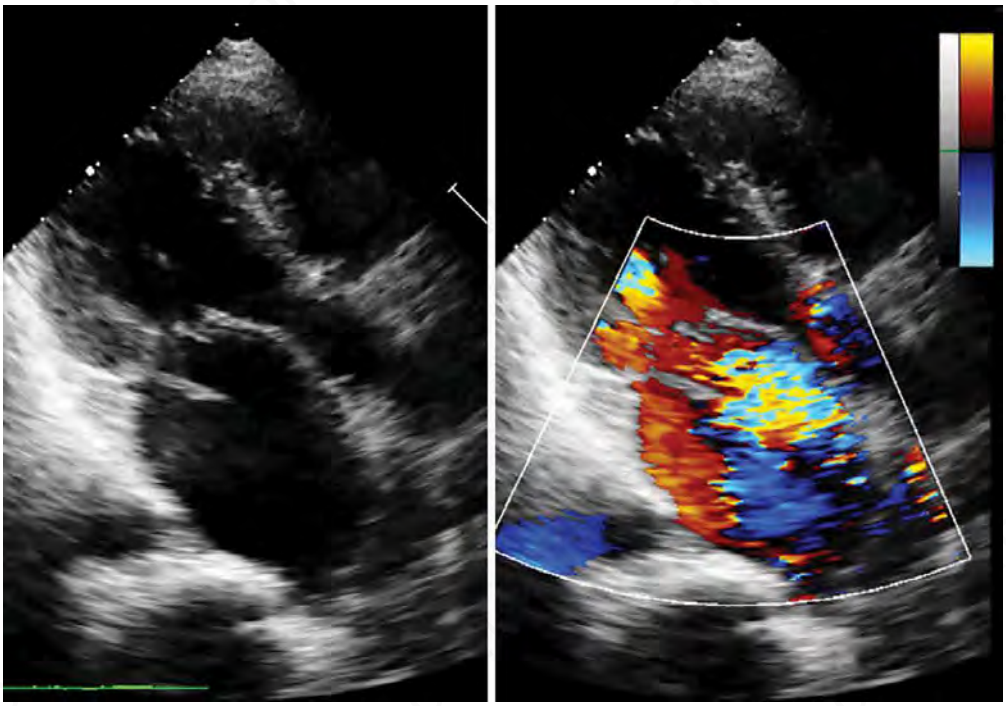


Fig. 86: 2D echo and Doppler in mitral valve prolapse (MVP)

Management

Medical

1. Reassurance regarding usually benign nature of the condition.
2. Endocarditis prophylaxis in patients with a murmur.
3. Drug treatment if arrhythmia.
4. Aspirin or anticoagulant in patients with emboli.

Surgical: Reconstruction or replacement of mitral valve in presence of severe regurgitation or evidence of progressive deterioration of LV function.

AORTIC VALVE DISEASE
AORTIC REGURGITATION

Causes

See Table 51 for the causes of aortic regurgitation.

Table 51: Causes of aortic regurgitation

A.	Valve leaflet disease:
	• Rheumatic fever
	• Congenital: Bicuspid valve, coarctation of aorta, in association with high (subaortic) VSD, sinus of valsalva (rupture)
	• Infective endocarditis (often on bicuspid valve).
	• Traumatic rupture of cusps.
B.	Aortic wall pathology:
	• Syphilis.
	• Inflammatory–Connective tissue disorder, e.g. ankylosing spondylitis, rheumatoid arthritis, SLE, Takayasu's disease, Reiter's syndrome.
	• Degenerative
	– Marfan's syndrome
	– Aortic root dissection
	– Arthropathy (senile thinning and stretching of aortic wall in absence of any other pathology).

Symptoms

1. Asymptomatic.
2. Dyspnoea – on exertion.
3. Angina pectoris – on heavy exertion or coinciding with onset of heart failure.
4. Palpitation – due to forceful heart beat. Unpleasant pulsation in head and neck may occur from very large stroke volume.
5. Syncopal attacks – may occur due to cerebral anoxia.

Signs

Cardiac palpation – Apical impulse displaced downward and to the left and thrusting in character. Diastolic thrill if syphilitic AR. ruptured sinus of Valsalva, or AR resulting from aortic dissection.

Murmurs

1. *Diastolic murmur* – High-pitched decrescendo murmur, maximal in early diastole, soft and blowing, with or after the second sound or masking the sound completely, maximum audibility over midsternum and to the left, transmission to the apex, best heard in held expiration with patient leaning forward (Fig. 87). In a few patients, the diastolic murmur has a rough or musical or sea-gull quality (A diastolic thrill may be felt along the left sternal border in such cases). If the murmur is best heard to the right of sternum, suspect dilatation of ascending aorta as in Marfan's syndrome, dissection of aorta or syphilis. The murmur may be even louder in high mid-left thorax, at apex, or in the midaxillary line, than in the sternal edge (Cole-Cecil murmur).

   A musical murmur may extend almost throughout diastole. Musical AR murmur may be due to: (a) Perforated leaflet as in infective endocarditis. (b) Everted leaflets (often syphilitic). (c) Rupture of an aortic sinus of valsalva.

   Diastolic murmur is very short in acute AR because the left ventricle which has had no time to dilate and hypertrophy, and rapid rise in LV diastolic pressure.

   Murmur can be increased in intensity by squatting or isometric exercise by handgrip or administering a vasopressor drug.
2. *Systolic ejection murmur* – due to increased stroke volume of left ventricle with often an ejection click.
3. *Austin flint murmur* – An apical low-pitched diastolic murmur may occur with severe AR. It is mainly due to the regurgitant jet vibrating the anterior mitral valve leaflet and displacing it backwards into the path of inflowing blood from left atrium. It must be differentiated from an organic mitral stenotic murmur (Table 52).

Fig. 87: Early decrescendo murmur of AR

4. *First sound at apex* – often soft or early because of premature closure of mitral valve.
5. *Second sound* at *base* – Single in severe AR because aortic component is absent.
6. *Third sound* – and apical pansystolic murmur of MR can commonly be heard as the LV dilates.

Peripheral – Due to wide pulse pressure

- *Collapsing (water hammer) pulse* – It may be absent if:
  (a) Associated mitral or aortic stenosis.
  (b) Hypertension.
  (c) Marked myocardial degeneration.
- *Visible arterial pulsations* – in neck (dancing carotids, Corrigan's neck sign).
- *Head bobbing* with each heartbeat (de Musset's sign).
- *Hill's sign* – Increase in femoral artery pressure over brachial artery pressure of more than the normal difference of 20 mm. Hg. Larger the pressure difference, more severe the degree of AR.

Table 52: Differentiating between AR with Austin Flint murmur and AR associated mitral stenosis

	AR with Austin Flint murmur	*AR with associated mitral stenosis*
Sex	More frequent in males	More frequent in females
Haemoptysis	Almost never	Strong evidence for mitral stenosis
Rhythm	Sinus	A. fibrillation common
Mitral 1st sound	Usually faint	Usually loud
P_2	Normal or increased	Usually loud
Opening snap	Absent	Present
Apical diastolic murmur	Usually early and mid-diastolic	Often presystolic accentuation
Apical gallop	Present	Absent with significant MS
Diastolic pressure	60 mm or less	Usually normal
Atrial fibrillation	Uncommon	May occur
LA enlargement on ECG or X-ray	Not seen	Seen
Calcification of mitral valve	None	May be seen
Amyl nitrite inhalation	Murmur decreases	Murmur louder
Echocardiography	Mitral valve normal and no significant Doppler gradient across it	Stenotic mitral valve

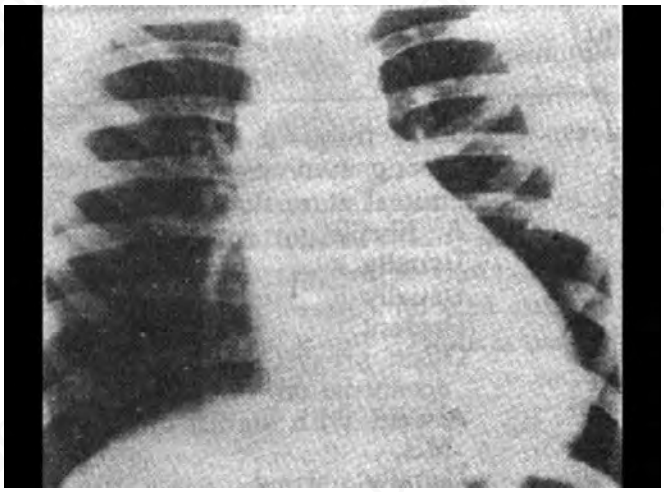


Fig. 88: Dilated left ventricle and prominent aorta due to chronic aortic regurgitation

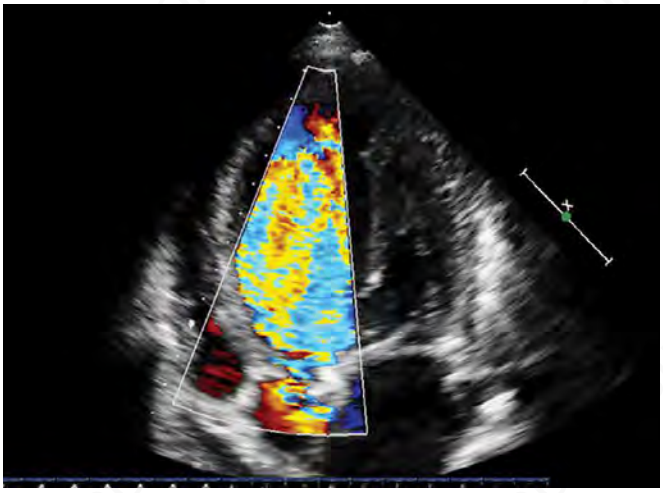


Fig. 89: Aortic regurgitation

- *Visible capillary pulsation* – in the nail beds (or mucous membrane of mouth) (Quincke's sign).
- *Pistol shot sounds* – over the femoral arteries (Traube's sign).
- *Duroziez's sign* – Diastolic murmur following distal compression of femoral artery.
- *Uvular pulsation* (Müller's sign)
- *Landolfi's sign* – Change in size of pupils with each cardiac cycle
- *Light house sign* - Alternate pallor and flushing of capillary pulsations on forehead and face.
- *Becker's sign* - Retinal artery pulsation
- *Mayne sign* >15 mm Hg fall in diastolic BP with elevation of the arm compared to the arm in normal position.
- *Gerhardt's sign* – Pulsations of an enlarged spleen
- *Rosenbach sign* – Pulsations of the liver

Clinical manifestations of a severe AR:

1. Prominent symptoms.
2. Peripheral signs well marked.
3. Difference of systolic BP between upper and lower extremities > 60 mm Hg.
4. Long duration of diastolic murmur. Duration however does not necessarily indicate severity; when the aortic valve is destroyed, the pressure equilibrates early in diastole and the murmur is brief.
5. Very low diastolic B.P
6. LV enlargement ++
7. Aortic S_2 inaudible
8. Retinal arterial pulsation
9. Pulses bisferiens (best felt in the carotids)

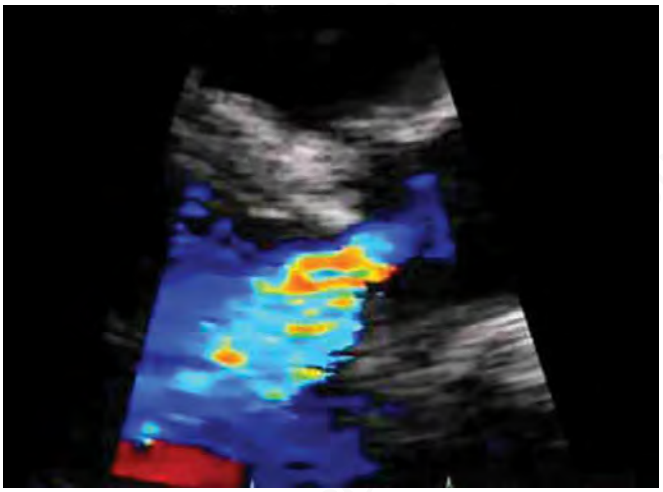


Fig. 90: Aortic regurgitation

Investigations

- *ECG* – Left ventricular hypertrophy, with diastolic overload pattern in severe regurgitation.
- *Chest X-ray* – Enlargement of the left ventricle, with 'duck-back' shape of left border (Fig. 88). Ascending aorta shows uniform enlargement.
- *Echocardiography* – is vital for examining aortic valve, determining size of aortic root and assessing LV function. Aetiology of AR can thus be established. Severity of regurgitation can be established from Colour Doppler study (Figs. 89 to 91).

Fluttering of anterior leaflet of mitral valve occurs when a regurgitant stream is directed posteriorly.

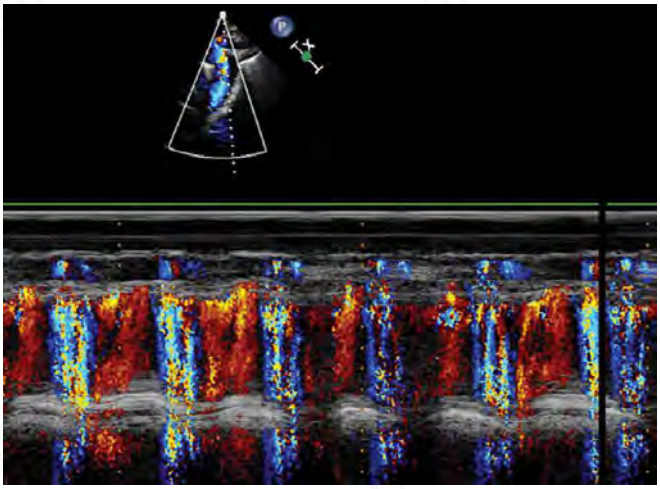


Fig. 91: Aortic regurgitation

Vibrations caused by the regurgitant stream may be seen on anterior mitral leaflet.

- *Cardiac catheterization* – has been supplanted by echocardiography. In adult patients, however, coronary angiography is undertaken before valve surgery and to perform aortography and left ventriculography.
- *Blood tests* – Treponemal serology and determination of inflammatory indices in patients with aortic wall disease.

Differential Diagnosis

1. Rheumatic aortic incompetence
2. Syphilitic aortic incompetence

   See Table 53 for the differences between rheumatic and syphilitic aortic regurgitation.
3. Atherosclerotic incompetence – Old age, angina common. Calcification of aortic knuckle and of the aortic valve. Some degree of aortic stenosis common.
4. Infective endocarditis– Changing murmurs, fever, anaemia, enlargement of spleen, embolic phenomena, hematuria and petechiae, clubbing and positive blood culture.
5. Congenital – Young patient, gross regurgitation, presence of some other congenital lesion.
6. Traumatic rupture of aortic cusp – Sudden onset of dyspnoea following fall or accident; loud, harsh and at times musical (seagull) aortic diastolic murmur, often accompanied by a thrill.
7. Marfan's syndrome – Aortic insufficiency due to process of degeneration involving aorta. Slender body build, abnormal height with disproportionately long bones especially fingers (arachnodactyly), high arched palate, hyperextensible joints, kyphoscoliosis and displacement of the lens.
8. Pulmonary regurgitation – Table 54 gives differences between aortic and pulmonary regurgitation.
9. Murmur of Anterior Descending Coronary Artery Stenosis (with moderate obstruction). High pitched crescendo-decrescendo diastolic murmur, most easily audible with patient sitting up. Murmur, disappears after myocardial infarction or aortocoronary bypass surgery.

   For differential diagnosis of diastolic murmurs: Refer

Table 53: Differences between rheumatic and syphilitic aortic regurgitation

Rheumatic AR	*Syphilitic AR*
History:	
More common before 30	More common after 30
History of rheumatic fever	History of syphilis
Duration may be long	Short duration or history
Angina pectoris rare	Angina pectoris common and earlier
Examination:	
Precordium may be prominent	No precordial prominence
Murmur best heard in third left	Murmur heard best over 2nd right
space, usually soft and low pitched and conducted better down left side	space, usually loud and harsh and conducted better down right side
AS may be associated	Pure aortic regurgitation
Diastolic thrill very rare	Diastolic thrill not uncommon
AR not so gross therefore	Peripheral vascular signs marked
peripheral signs not marked	because AR usually gross
Slight or no difference in brachial or carotid pulsations	Appreciable difference in strength of carotid or brachial pulse on either side
Mitral valve may be affected	No involvement of mitral valve.
Investigations:	
Blood: Syphilis serology negative	Syphilis serology positive
X-ray: No calcification or irregularity of aorta	Calcification confined to ascending aorta. Irregularity of aorta. No calcification of aortic valve
ECG: Heart block rare	Heart block common

Management

- *Medical:* (a) Prophylaxis against infective endocarditis. (b) Therapy of heart failure if it develops.

Table 54: Differences between aortic and pulmonary regurgitation

AR	PR (Graham Steell murmur)
Water hammer pulse and peripheral signs	No peripheral signs
LV hypertrophy	RV hypertrophy
Murmur does not change on respiration	Murmur increases with inspiration
Murmur returns to normal intensity 4–5 beats after valsalva strain	Murmur resumes pre-valsalva loudness immediately

- *Surgical:* Replacement of aortic valve should be performed before heart failure can develop. Serial evaluation of end-systolic dimensions should be made and surgery considered when this (on M-mode echocardiography) exceeds 55 mm.

AORTIC STENOSIS

Causes

Table 55 lists the causes of aortic stenosis.

Table 55: Causes of aortic stenosis

I.	Valvar stenosis
	• Congenital malformation (most common cause of isolated AS).
	• Calcification of normal valve.
	• Inflammatory fusion – Rheumatic fever (lesion is nearly always mixed stenosis and regurgitation).
	• Worn bicuspid valve
II.	Subvalvar stenosis
	1. *Fixed type* – Due to fibrous ring, fibrous ring plus moderate muscular obstruction, or rarely anomalous insertion of mitral valve.
	2. *Hypertrophic type* – due to HOCM.
III.	Supravalvar stenosis
	Due to ridge of fibrous tissue at upper border of sinuses of valsalva.

Symptoms

1. *No symptoms* – Most well compensated of valvular diseases. Symptoms occur when the valve orifice is reduced to 1 cm^2 or less, the resting peak systolic pressure difference between LV and aorta is at least 50 mm Hg.
2. *Angina* – Due to:
   - Increased oxygen demand by the hypertrophied myocardium.
   - Shortening of diastole, the time when the coronary arteries fill, caused by prolonged ventricular ejection time.
   - Squeezing effect on coronary arteries by high LV systolic pressure.
   - Involvement of coronary ostia in the stenotic process.
3. *Syncope* – Syncopal spells beginning after onset of left ventricular failure are often brought on by little if any effort and are of grave significance.
4. *Exertional dyspnoea* – Often first symptom. Orthopnoea and paroxysmal dyspnoea follow as result of left ventricular failure.
5. *LV failure* – Dyspnoea, orthopnoea, pulmonary oedema, most frequent when standing.

Signs

1. *Sustained and heaving cardiac impulse.*

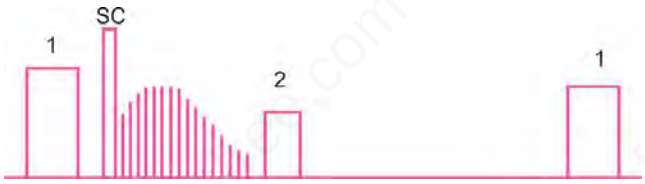


Fig. 92: Ejection systolic murmur and systolic click in aortic stenosis

2. *Systolic thrill* – in second right interspace and also sometimes along the right cervical vessels.
3. *Ejection systolic murmur* – in aortic area, rough or harsh, beginning slightly after the first sound, rising to a peak in midsystole and tapering off before the second sound (Fig. 92). Sometimes the murmur may be loudest at the apex, because the murmur sounds higher pitched at the apex (Gallavardin phenomenon) as a result of selective radiation of higher frequencies. Occasionally, the murmur becomes softer as one goes down from aortic to mitral area and then again increases in intensity (hour-glass conduction). In elderly, the murmur of AS is frequently a musical, cooing murmur localised to the apex. It is frequently audible over carotid arteries. With increasingly severe stenosis prolonging the LV ejection time, the murmur becomes longer and attains its peak later. The murmur becomes quieter in advanced disease when the force of LV contraction is weakened.
4. *Ejection systolic click* – precedes the murmur in many cases. It is caused by sudden tension of a pliable dome-shaped stenotic valve at the time of its opening. Disappears with calcification of the valve.

5. *Quiet 1st heart sound.*
6. *2nd heart sound*– Delayed with reversed splitting in severe stenosis, or faint or absent. The aortic component of S_2 is absent when the valve is rigid and the pulmonary component may be inaudible; mitral closure is often quiet. Thus only a murmur is heard, and this may be judged pansystolic because of absence of heart sounds.
7. *Atrial gallop*– may be heard over the left ventricle and in patients under 40 is a reliable evidence of severe stenosis.
8. *Slow rising sustained pulse (pulsus parvus et tardus).* When a small wave is felt along the upstroke, the pulse is called anacrotic.
9. *BP* – Low systolic with narrowed pulse pressure in severe AS.

Investigations

ECG – LV hypertrophy common, proportional to degree of stenosis. Conduction defects common.

Chest radiograph (Fig. 93) – (a) Prominent rounded left ventricle. (b) Poststenotic dilatation especially if stenosis is congenital in origin. (c) Aortic valve calcification.

Echocardiography – Both M-mode and CSE will show the stenosed valve. The valve area may be estimated from cross-sectional images and the gradient across the valve assessed from a Doppler study (Figs. 94 to 96).

Left heart catheterization – is indicated in presence of symptoms or development of LV hypertrophy with ST-T changes in ECG. Useful for determining gradient across the valve (50 mm Hg: Moderate stenosis, 70 mm Hg: Severe stenosis), measuring cardiac output, assessing LV function and to exclude co-existing coronary disease.

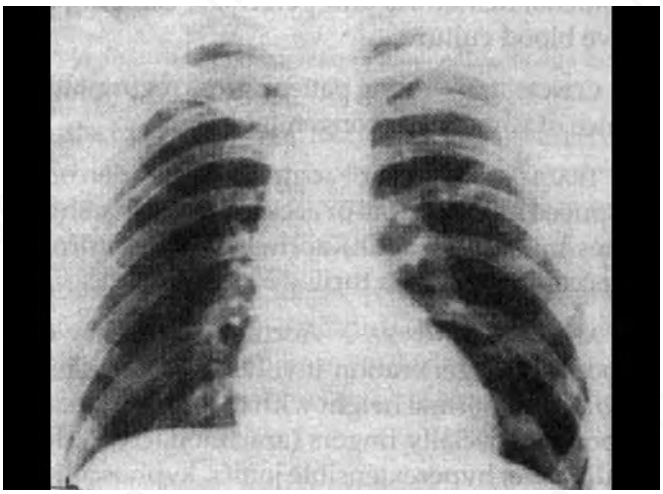


Fig. 93: Aortic stenosis. Poststenotic dilatation of the ascending aorta seen at the right heart border. Left ventricular silhouette appears convex and with the apex extending below the diaphragm

Subvalvar Stenosis

1. Absence of aortic ejection click with no calcification of aortic valve.
2. Diastolic murmur due to AR more common.
3. Mid-diastolic murmur at apex.
4. Heart size tends to be larger.
5. Ascending aorta usually not dilated.

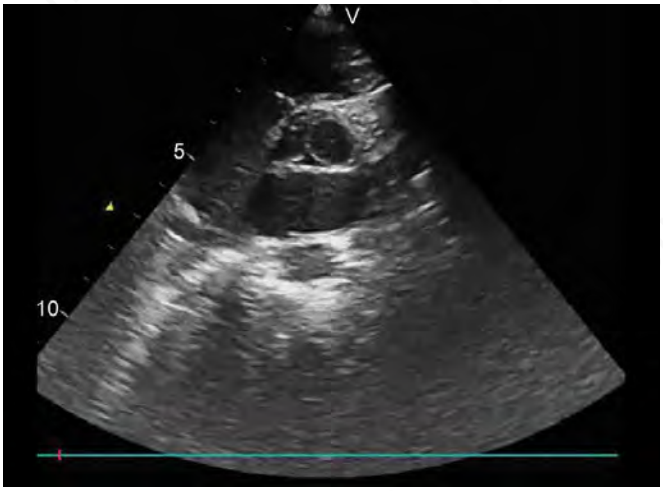


Fig. 94: 2D echo aortic stenosis

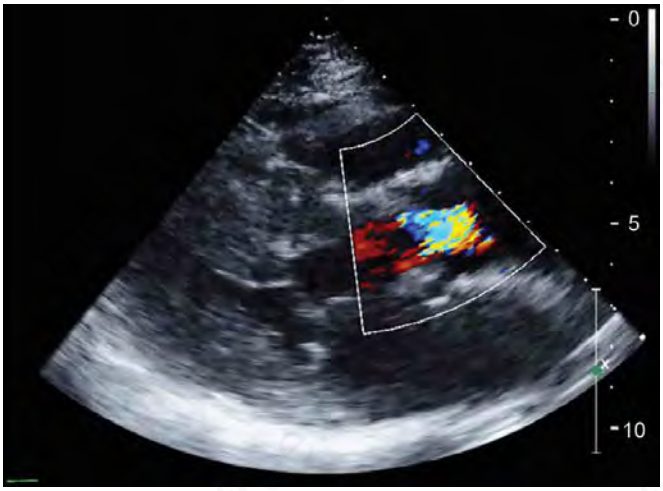


Fig. 95: Echo Doppler aortic stenosis showing turbulent flow

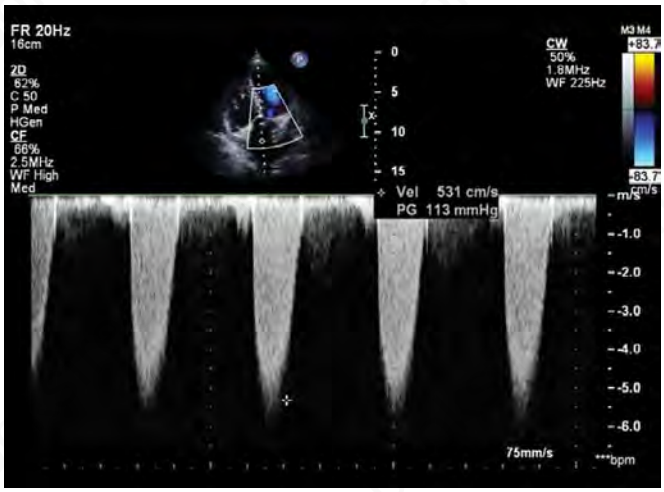


Fig. 96: Echo Doppler aortic stenosis

Supravalvar Stenosis

1. Characteristic facies with physical and mental retardation.
2. Systolic BP usually higher in right arm than in left arm due to stenosis of one or more branches of the aortic arch.
3. Absence of aortic ejection click.
4. No post-stenotic dilatation of aorta.

See Table 56 for the differences between valvular, subvalvular and supravalvular aortic stenosis and Table 57 for differences between HOCM and aortic valvular stenosis. Also see Differential Diagnosis of systolic murmurs.

Management

1. *Prophylaxis*–against infective endocarditis.
2. *Balloon valvuloplasty* – gives transient relief and is indicated in elderly patients with advanced symptoms.
3. *Aortic balloon valvotomy* – is confined to congenital AS and may be necessary if – (a) Total fusion of two valve cusps. (b) ECG changes of LV hypertrophy. (c) Significant pressure drop across aortic valve. (d) Eventual development of LV decompensation. (e) Risk of sudden death.

BICUSPID AORTIC VALVE

Bicuspid aortic valve is a minor congenital anomaly. Normal symmetry of aortic valve is disturbed because one leaflet is larger than the other two, the commissures of which are fused to some extent. More common in males.

Table 56: Differences between valvular, subvalvular and supravalvular aortic stenosis

Clinical features	*Valvar*	*Sub-valvar*	*Supra-valvar*
Physical appearance	Normal	Normal	Elfin facies
Pulse	Slow rise and sustained peak		Right brachial and carotid more than left
Ejection click	Typical	Rare	Rare
Maximum intensify of ejection murmur	1st or 2nd right interspace		1st right interspace and over right carotid
Murmur of AR	Common	Common	Uncommon

Table 57: Differences between HOCM and aortic valvular stenosis

Clinical signs	*HOCM*	*Aortic valvar stenosis*
Double apex impulse	Common	Less common
Presystolic gallop	Common	Less common
Single 2nd sound	Less common	Common
Paradoxical splitting of 2nd sound	Common	Less common
Systolic thrill	Not common	Common
Systolic murmur	Along left sternal border and at apex	2nd right interspace radiating to neck
Diastolic murmur of AR	Rare	Common
Carotid pulse	Visible, rapid upstroke	Invisible, slow upstroke
Valsalva manoeuvre	Murmur louder	Murmur softer
	Aortic stenosis	*Pulmonary stenosis*
Effect of respiration	Murmur decreases on inspiration	Murmur increases on inspiration
Site of murmur	Maximal intensity in 2nd right interspace	Murmur maximal along left sternal border
Ejection click	No change on inspiration	Decreases or disappears on inspiration

Clinical Features

- Ejection click
- Soft ejection murmur
- Short, high pitched diastolic murmur sometimes
- Loud A_2

Importance of Diagnosis

Valve may be affected by endocarditis, hence antibiotic prophylaxis necessary.

Tear on the valve leaflet is greater than in normal valve so that significant stenosis and/or regurgitation may develop by middle life.

TRICUSPID VALVE DISEASE
TRICUSPID REGURGITATION

Causes

Causes of tricuspid regurgitation are listed in Table 58.

Symptoms: Tiredness on effort, hepatic pain on exertion, peripheral oedema, disturbing pulsations in neck.

Signs

- Systolic pulsation in jugular venous pulse.
- Pansystolic murmur in tricuspid area that increases with inspiration or exercise.
- Atrial fibrillation common.
- Pulsatile liver
  - *EGG* – RV hypertrophy and often AF.
  - *X-ray* – Enlargement of RA and RV.
  - *Echo* – may reveal systolic prolapse, ruptured chordae, or vegetations. Doppler echo can give estimate of severity of regurgitation and systolic pressure in RV. If leaflet thickening seen on CSE, lesion is organic (Fig. 97).

Treatment

Functional TR – Bed rest, digitalis, diure-tics, vasodilators.
Organic TR - Replacement of valve.

TRICUSPID STENOSIS

Causes:

1. Rheumatic usually associated with MS. 2. Congenital – Tricuspid atresia and Ebstein's disease. 3. Carcinoid tumour. 4. Functional due to right atrial tumour.

Table 58: Causes of tricuspid regurgitation

A.	Functional – more common.
1.	RV failure from any cause.
2.	Rheumatic mitral disease.
3.	Pulmonary stenosis.
4.	Pulmonary hypertension idiopathic, or secondary to lung disease, thromboembolism, or congenital shunting.
B.	Organic – rare.
1.	Congenital usually associated with Ebstein's anomaly.
2.	Traumatic due to rupture of right ventricular papillary muscle.
3.	Carcinoid disease.
4.	Rheumatic.
5.	Infective endocarditis in drug addicts.
6.	Lupus erythematosus.
7.	Right atrial myxoma.
8.	Endomyocardial fibrosis.
9.	A-V cushion defects

Symptoms

Hepatic pain on exertion, peripheral oedema, dyspnoea on exertion.

Signs

JVP raised. With sinus rhythm giant 'a' waves. First sound may be loud. Diastolic murmur at left sternal edge. Liver enlarged and may show presystolic pulsations.

ECG – RA hypertrophy but no RVH.

X-ray – Enlarged RA, lung fields usually clear.

Treatment

Replacement of the valve.

PULMONARY VALVE DISEASE
PULMONARY REGURGITATION

Causes

- *Congenital* – With tetralogy of Fallot, Marfan's syndrome, Eisenmenger's syndrome, isolated, with PDA, idiopathic dilatation of pulmonary artery.
- *Acquired* – With idiopathic pulmonary hypertension, MS, IE, rheumatic fever, syphilis, carcinoid syndrome, aneurysm of pulmonary artery, pulmonary hypertension.

Signs

Early diastolic murmur similar in quality to that of AR, conducted down the left sternal border. Associated signs of pulmonary hypertension.

ECG – Right ventricular hypertrophy.

X-ray – Enlargement of pulmonary artery.

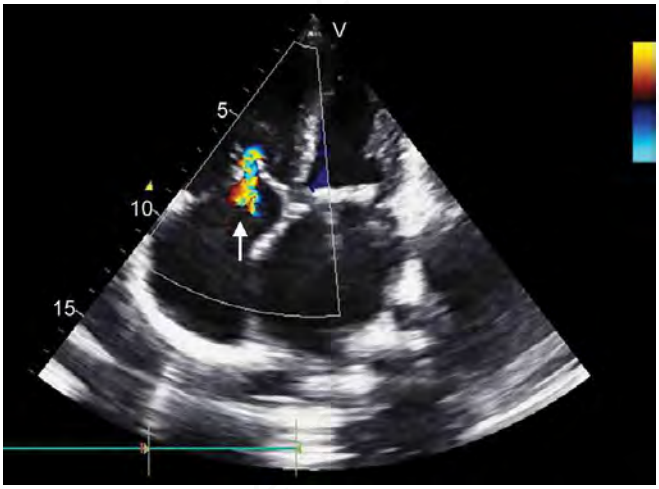


Fig. 97: 2D echo apical 4-chamber view showing regurgitant jet of tricuspid regurgitation

PULMONARY STENOSIS

Aetiology

1. Usually congenital. 2. May be associated with carcinoid syndrome. 3. Rarely associated with Kallmann's syndrome (gonadotrophin deficiency secondary to LHRH deficiency, with anosmia).

Signs

Systolic thrill in second left space with ejection mid-systolic murmur loudest on inspiration (see congenital heart disease).

7. INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is an illness caused by microbial infection of the cardiac endothelial surface. *Acute bacterial endocarditis* (ABE) is caused by virulent organisms and runs its course over days to weeks. *Subacute bacterial endocarditis* (SBE) is caused by organisms of low virulence and runs its course over weeks or months.

Risk of developing infective endocarditis is give in Table 59.

Factors determining site of infection – The common factor is a high velocity jet of blood which damages the endocardium. Mild valvular abnormalities are more susceptible to infection than severe abnormalities. A regurgitation stream and a large pressure drop across a small orifice increase likelihood of infection, e.g. mild AR or MR, or small VSD. Hypertrophic cardiomyopathy is associated with pressure gradients with high velocity jets, and infection is not uncommon.

Table 59: Risk of developing infective endocarditis

Relatively high risk
• Prosthetic heart valves.
• Aortic valve disease
• Mitral regurgitation + stenosis
• Congenital heart disease
– Persistent ductus arteriosus
– Ventricular septal defect
– Coarctation of aorta
– Marfan's syndrome
– Cyanotic congenital heart diseases.
• Previous infective endocarditis.
Intermediate risk
• Mitral valve prolapse
• Mitral stenosis
• Tricuspid valve disease
• Pulmonary valve disease
• Asymmetrical septal hypertrophy
• Calcific aortic sclerosis
• Non-valvar intracardiac prosthetic implants
Very low risk
• Atrial septal defect
• Atherosclerotic plaques
• Post myocardial infarction thrombi, atrial thrombi and ventricular aneurysms
• Syphilitic aortitis
• Cardiac pacemakers
• Surgically corrected cardiac lesions (without prosthetic implants)
• Valve bearing conduits, or indwelling plastic catheters for hydrocephalus in children.

INFECTION OF NATIVE VALVES

Massive infection of right side of heart in drug addicts who inject themselves IV under unsterile conditions. Patients with normal valves are more often infected with pyogenic organisms than those with chronic valve disease, possibly because endocarditis caused by pyogenic organisms follows direct bacterial implantation on the valve rather than infection of pre-existing platelet fibrin vegetation.

SURGICAL ENDOCARDITIS

Surgical endocarditis may follow any type of surgery and is often caused by Staph. epidermidis. *Prosthetic valve endocarditis* (PVE) can be divided into:

(a) *Early PVE* – where organisms gain access during surgery or through wound infection and which usually presents within 1–2 months after surgery.

(b) *Late PVE* – caused by the same range of organisms which invade native valves.

The left side of the heart is much more commonly involved because of higher oxygen saturation promoting growth of aerobic bacteria, and the higher pressure causing more intimal damage.

Right-sided endocarditis is not limited to injection drug users. Modern imaging techniques like PET scanning are helpful in localizing the focus of infection in a patient with unexplained bacteraemia.

CAUSATIVE ORGANISMS

- **Bacterial** – Common – Streptococcus viridans. Streptococcus faecalis and Staphylococcus epidermidis. Staphylococci are common in early post-operative cases and among drug addicts. Uncommon – Pneumogono- or meningococcus, B. proteus, B. pyocyaneus, Gram-negative organisms from the bowel, and HACKE (Haemophilus spp., Actinobacillus spp., Corynebacterium spp., Eikenella corrodens, and Kingella spp.).
- **Non-bacterial** – (a) Rickettsial – Coxiella burnetii. (b) Fungal – Candida, monilia, aspergillus, histoplasma and torulosis. (c) Chlamydia type B agent of psittacosis.

PORTAL OF ENTRY

- Dental extraction or scaling
- Tonsillectomy
- Genitourinary and rectal procedures – Catheterization, D and C, sigmoidoscopy
- Bedsores
- Puerperal infection
- Cardiac surgery or cardiac catheterization
- Long-standing intravenous infusions
- IV drug taking in addicts
- Insertion of IUCD

PATHOPHYSIOLOGY

Ulceration of the valvular endocardial surface promotes bacterial adherence by two possible mechanisms:

1. Direct contact between blood and subendothelial components results in production of coagulum or a small clot. Pathogens associated with IE circulating in the blood stream as a result of transient bacteraemia bind avidly to the coagulum and in turn attract and activate monocytes to produce cytokines, resulting in progressive enlargement of an infected vegetation.
2. Local inflammation promotes cells to express transmembrane proteins that bind fibronectin. Pathogens such as Staph. aureus carry fibronectin binding proteins on the surface. Staphylococcal endocarditis is often seen in patients with normal valves, and microulceration are thought to be responsible for endocarditis by this mechanism.

MODES OF ONSET

1. Usually insidious with vague ill health and symptoms of fatigue, loss of appetite with or without pyrexia.
2. Influenzal onset with chills and sore throat.
3. Pyrexia of unknown origin.
4. Musculoskeletal syndrome with myalgia, joint pains, and at times fleeting arthritis like rheumatic fever.
5. Neurologic syndrome – May present as a case of focal neurological deficit due to cardioembolic stroke, meningitis, subarachnoid haemorrhage, hemiplegia, coma or convulsions.
6. Haematologic syndrome – Fever, anaemia.
7. Peripheral vascular disease – Gangrene.
8. Splenic infarct.
9. Congestive heart failure without obvious cause in elderly.
10. Unilateral blindness
11. Pneumonia
12. Kidney failure
13. Pleurisy

Atypical presentation is common in elderly or immunocompromised patients, in whom fever is often absent.

CLINICAL FEATURES

Sign of Infection

- **Fever** – variable, low grade. In acute endocarditis, hectic fever, rigors and extreme illness. No fever if CHF, chronic kidney failure, fungal endocarditis, prior antibiotic therapy, severe sepsis, or old age.
- **Anaemia** – Yellow muddy discolouration of skin.
- **Clubbing** – of fingers and toes occurs early.
- **Splenomegaly** – after about 6 weeks of illness. Sudden enlargement with tenderness and rub if infarction of spleen. Rarely gross splenomegaly.
- **Arthralgia** – Sudden transient pains in joints without any effusion.

Cardiac Signs

- **Murmur**
  - *Organic heart murmur* – due to valvular defect or congenital cardiovascular lesions.
  - *Alteration in intensity of murmur*
  - *Development of new murmurs* – due to perforation of ventricular septum, rupture of sinus of valsalva, acute MR or acute AR.
  - *Absence of murmur* – (a) Endocarditis involving mural thrombus complicating healed myocardial infarction. (b) Early acute endocarditis involving previously normal valve. (c) Tricuspid endocarditis, when it exists, may be murmur free.
- **Cardiac failure** – may occur due to toxic myocarditis. Rarely pericarditis, or coronary occlusion. In case of acute valvular regurgitation, pulmonary oedema will occur with little cardiac enlargement and with a sharp fall in cardiac output.

Systemic Embolism

Arterial

- *Cerebral* producing hemiplegia or mycotic aneurysms which may subsequently rupture.
- *Renal* causing colic and hematuria.
- *Retinal* with disturbing vision.
- *Of mesenteric arteries* causing acute abdominal pain; splenic infarction with sudden local pain and perhaps friction.
- *Peripheral vessel* resulting in gangrene of an extremity. Early prosthetic valve endocarditis emboli that occlude large vessels would suggest fungal endocarditis.

Pulmonary

Pulmonary (with left-to-right shunts or involvement of pulmonary valve). Recurrent pneumonitis (infective emboli cause abscesses) and arterial rupture.

Immunological

Skin

- *Thenar and hypothenar eminences*
  - Osler's nodes – Tender, pea-sized nodules on pads of fingers and toes. Often pale in the centre. May occur in crops. Fade after few days usually without breaking down or leaving any residue. Either due to minute emboli in superficial terminal vessels or due to vasculitis.
  - Janeway lesions – Large non-tender macules on palms and soles, it is vascular phenomenon due to septic embolization.
- *Skin and mucous membranes*
  - Petechial haemorrhages in palpebral conjunctivae, buccal and pharyngeal mucous membrane.
- *Subungual* – Splinter haemorrhages
- *Finger and toe tips* – Osler's nodes
- *Retina* – Roth spots – Lesions with a white centre and red edge. Boat-shaped hemorrhage
- *Renal* – Glomerulonephritis leading to kidney failure

COMPLICATIONS (CAUSES OF DEATH)

1. Acute valve perforation
2. Embolism and rupture of mycotic aneurysm
3. Kidney failure

INVESTIGATIONS

1. *Blood cultures* – In absence of recent or concurrent antibiotic therapy, the first 3 random blood cultures (2–4 hours apart) are positive in most patients, and blood culture is positive by third day in 90%.
2. *Urine* – Microscopic hematuria most common finding. Slight albuminuria and hyaline and granular casts also found.
3. *Haematology* – Normocytic normochromic anaemia, usually mild. May be raised ESR and raised C-reactive protein.
4. *Chest radiograph* – may be diagnostic in right sided endocarditis, with multiple shadows visible due to an embolic pneumonia.
5. *ECG* – Myocardial infarction seen on ECG may be due to coronary embolism, and a conduction defect may be due to development of an aortic root abscess.
6. *Echocardiography* – Higher sensitivity in identifying vegetation with TOE as compared to TTE. (a) Vegetations: An echodense structure attached to the valve or its supporting structures, or lying in the track of a turbulent jet, which is irregular in shape. (b) Leaflet

Table 60: Modified Duke criteria for the diagnosis of infective endocarditis

Pathological criteria
• Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments, or intracardiac abscess content).
Major criteria
• Two positive blood cultures showing typical organisms consistent with infective endocarditis, such as *Streptococcus viridans* and the HACEK group OR
• Persistent bacteraemia from two blood cultures taken >12 hours apart or three or more positive blood cultures where the pathogen is less specific, such as *Staphylococcus aureus* and *Staph epidermidis* OR
• Positive serology for *Coxiella burnetii, Bartonella* species, or *Chlamydia psittaci* OR single culture positive for *Coxiella burnetii*
• Positive molecular assays for specific gene targets
• Positive echocardiogram showing oscillating structures, abscess formation, new valvular regurgitation, or dehiscence of prosthetic valves
Minor criteria
• Predisposing heart disease or intravenous drug abuse.
• Fever >38°C
• Immunological phenomena such as glomerulonephritis, Osler's nodes, Roth spots, or positive rheumatoid factor
• Microbiological evidence not fitting major criteria
• Elevated C reactive protein or erythrocyte sedimentation rate
• Vascular phenomena such as major emboli, splenomegaly, clubbing, splinter haemorrhages, petechiae, or purpura
Definite infective endocarditis
• Pathological criteria positive OR
• Two major criteria OR
• One major and two minor criteria OR
• Five minor criteria

perforation is best seen as regurgitant jet on colour flow mapping. (c) Annular and periprosthetic echolucent spaces (abscesses) and fistula formation.

DIAGNOSTIC CRITERIA

The diagnosis of infective endocarditis requires a multifaceted approach involving clinical suspicion and examination, laboratory investigations by means of inflammatory markers and microbiological analysis, and imaging with echocardiography. The modified Duke's criteria unite these modalities to arrive at an accurate diagnosis (Table 60).

MANAGEMENT

A. ***Antibiotics***

- *Principles* – (a) Should be given early before irremediable complications occur. (b) Adequate dosage, the amount depending on the sensitivity of the organism to the antibiotic. (c) Bactericidal antibiotics such as penicillin (including ampicillin derivatives), cephalosporins and aminoglycosides must be used alone or in combination. (d) Must be continued long enough to sterilize all vegetations and all possible embolic foci, usually 6–8 weeks.

Initial Therapy – Choice of antibiotic is determined initially by deducing the infective organism, and the antibiotic can, if necessary, be adjusted later according to laboratory guidance. Two antibiotics should be used in combination for their synergistic effect and to deter development of resistance.

If suspected Staphylococcal infection – Flucloxacillin 12–15 g/24 hours and gentamicin. To ensure high peak concentrations, antibiotics are best given by IV bolus into a central venous line in subclavian or jugular vein.

Specific therapy – When sensitivities are known (Table 61).

Duration of treatment – In absence of complications treatment is usually continued for 6 weeks, but the duration depends on the infecting organism, duration of symptoms before diagnosis, rapidity of response and presence or absence of prosthetic valve or material.

Special problems

Negative blood cultures – Causes:

1. Patient has received antibiotics in recent weeks.
2. Infection by cell-dependent or fastidious organisms including Legionella, Coxiella, the HACEK group, and fungus such as Candida, Histoplasma, and Aspergillus species. Serological testing can be particularly useful for investigating the possibility of Coxiella burnetii and Bartonella infection.
3. Infection due to Streptococcus spp. with special growth requirements.

Penicillin allergy – Patients with a history of penicillin reactions and those who develop sensitivity during the course of treatment should be given IV erythromycin lactobionate 4 g/24 hours with oral rifampicin 10 mg/kg/24 hours.

Persistence of fever – If fever remains uncontrolled with presumably adequate treatment, possibilities are – (1) Drug hypersensitivity (rash and other manifestations). (2) Local reaction at injection site. (3) Persistence of focus of infection e.g. splenic or other abscess, dental apical granuloma. (4) Bacterial L-forms resistant to usual antibiotics may have developed. (5) Increased bacterial resistance can be acquired during treatment due to inadequate initial treatment. (6) Unsuspected multiple infections. (7) Another organism may have been acquired during therapy especially if indwelling IV lines are used.

Table 61: Antibacterial regimes for endocarditis

Organism	*Regimen*
Strep. viridans	Penicillin G 4 million U q6h + Gentamicin 1 mg/kg q12h or Ceftriaxone 2 g od
Enterococci	Penicillin G or Ampicillin 2 g IV q6h or Vancomycin 15 mg/kg q12h + Gentamicin 1 mg/kg q8h (or Tobramycin 3–5 mg/kg q6h)
Strep. bovis, Strep. faecalis and other penicillin-resistant Strepto.	Vancomycin 10 mg/kg q12h IV Ampicillin 8 g/24 h + Gentamicin 1 mg/kg q8h or Vancomycin 15 mg/kg q12h + Gentamicin 1 mg/kg q8h
Staph. aureus	Flucloxacillin 12–16 g/24 h + Gentamicin 1 mg/kg q8h or Netilmicin 6 mg/kg q8h
Staph. epidermidis	Fusidic acid 500 mg q8h + IV Vancomycin 1 g/12h or Cefazolin 2 g IV q8h
HACEK group	Ampicillin 2 g IV q4h + Gentamicin 1 mg/kg q12h or Ceftriaxone 1–2 g IV od
Culture-ve prosthetic valve endocarditis	Vancomycin + Gentamicin + Ampicillin, or Cefoperazone 1–2 g IV b.d.
Coxiella burnetii	Doxycycline (100 mg PO q12h) + hydroxychloroquine (200 mg PO q8h), both for 18 (native valve) or 24 (prosthetic valve) months

Infection by cell-dependent organisms: Chlamydia– Doxycycline 4 g/day to start with, then 1 g/day, and replacement of infected valve. The drug can be continued indefinitely if infection cannot be eradicated or, if the valve is sound enough not to require replacement.

Fungal endocarditis – usually caused by Candida (Large friable vegetations seen on echo). IV Amphotericin (test dose 5 mg over 2 hours; gradual increase over 7 days to 1 mg/kg/day, to maximum of 2 g) plus oral Flucytosine 100-200 mg/day in 4 divided doses. Surgical excision of prosthetic valves or material essential.

Monitoring antibiotic blood levels – It is advisable that the peak plasma antibiotic concentration should be at least eight times the minimum in vitro bactericidal concentration. Both the minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of the antibiotics administered should be determined. The two titres are normally the same and the development of bacterial tolerance can be recognised if the MBC becomes much higher than the MIC. Blood levels of the aminoglycosides should always be measured.

B. ***General measures*** – (a) Complete rest in bed. (b) High protein diet with added vitamins and iron. (c) Small repeated blood transfusions if severe anaemia

C. ***Surgical measures*** – Indications for surgical interventions in endocarditis are given in Table 62.

PROPHYLAXIS

Endocarditis prophylaxis is described in Table 63.

- **Noninfective endocarditis** refers to sterile platelets and fibrin formation on cardiac valves and adjacent endocardium in response to trauma, circulating immune complexes, vasculitis or a hypercoagulable state.
- **Non-bacteraemic thrombotic endocarditis:** Vegetations tend to form on congenitally abnormal valves or those damaged by rheumatic fever. It often occurs in malignancy and wasting disorder, e.g. TB, uraemia, AIDS**.** The initiating factor in NBTE is not known. Endothelial damage by circulating cytokines (e.g.

Table 62: Indications for surgical interventions in endocarditis

• Infection cannot be controlled medically
• Acute or chronic heart failure as a result of valve destruction especially aortic valve, septal defects, aneurysms and major emboli
• Early prosthetic valve endocarditis
• In Candida infection removal of prosthesis is essential
• Infected tricuspid valve (common in drug addicts) may be removed without replacement
• Detection of abscess formation by CSE since it indicates advanced infection
• Infection by resistant organism such as fungi, Coxiella or Staph. epidermidis, or by a rapidly destructive organism such as Staph. aureus
• Large vegetations (>10 mm) on mitral valve with high embolic potential

Table 63: Endocarditis prophylaxis

Clinical situation	*Antibiotic*	*Dose*
Standard prophylaxis	Amoxicillin	2 g PO 1 hr before procedure
Unable to take oral medications	Ampicillin	2 g IV or IM within 30 min before procedure
Penicillin allergy	Clindamycin or Cephalexin or cefadroxil or Azithromycin or clarithromycin	600 mg PO 1 hr before procedure 2 g PO 1 hr before procedure 500 mg 1 hr before procedure
For Genitourinary/Gastrointestinal (excluding oesophageal procedures)		
High-risk patients	Ampicillin plus gentamicin (within 30 min of starting procedure) followed by ampicillin or Amoxicillin (6 hr later)	2 g IM or IV 1.5 mg/kg IV or IM (not to exceed 120 mg) 1 g IM or IV
High-risk patients allergic to penicillin	Vancomycin plus gentamicin (within 30 min of starting procedure)	1 g PO or 1 g IV over 1–2 hr 1.5 mg/kg IV or IM (not to exceed 120 mg)
Moderate-risk patients	amoxicillin or ampicillin	2 g PO 1 hr before procedure 2 g IV or IM within 30 min of starting procedure
Moderate-risk patients allergic to penicillin	Vancomycin	1 g IV over 1–2 hr completed within 30 min of starting the procedure

tumour necrosis factor or interleukin which can be increased in malignancy or chronic wasting diseases might trigger platelet deposition

- **Libman-Sacks endocarditis:** Develops due to circulating immune complexes, vegetations 3–4 mm in size and composed of degenerating valve tissue. Most common on ventricular surface of mitral valve may become a nidus for infection leading to infective endocarditis seen in SLE.

8. CARDIOVASCULAR SYPHILIS

Aetiology – *Age* – Peak incidence between 35 and 50. *Sex* – Males predominate. *Latent period* – after primary syphilis 15–25 years.

CLINICAL MANIFESTATIONS

I. **Aortitis** – Suggestive diagnostic criteria:
   - Dilatation of ascending aorta.
   - Tambour quality of aortic second sound in absence of hypertension or atherosclerosis.
   - Systolic aortic murmur.
   - Burning retro-sternal pain and breathlessness.
   - Calcification of ascending aorta (in late stages).

II. **Angina pectoris** – Due to aortitis affecting nearby coronary ostia. Syphilitic angina pectoris differs from angina of atherosclerotic origin thus –
   - Duration of attacks tends to be longer.
   - Nocturnal attacks are more frequent.
   - Sublingual nitroglycerine is not so effective.
   - Myocardial infarction is uncommon, but is frequently fatal.

III. **Aortic regurgitation** – Refer

IV. **Syphilitic aortic aneurysm** – occurs most often in ascending aorta.

Aneurysm of ascending aorta – (Aneurysm of signs) (Fig. 98).

Symptoms

Rare: Pain on right side of chest or back. Feeling of engorgement of face and arms on stooping. Dyspnoea or paroxysms of cough (gander or bovine cough). Occasionally haemoptysis may be the first symptom.

Signs

Inspection – Face and neck of high colour. Swelling of one or both arms and engorged veins on front of chest. Unilateral finger clubbing may be seen usually right-sided. Visible pulsating mass may be seen in 2nd or 3rd right interspace, and there may be exaggerated pulsations in the right sternoclavicular joint or in the episternal notch.

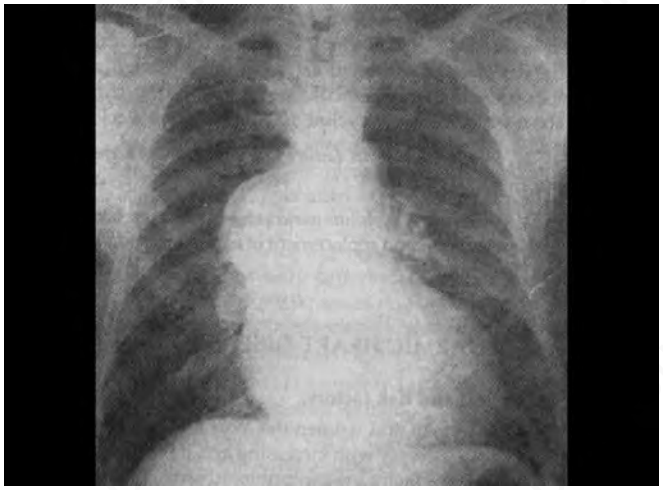


Fig. 98: Aneurysm of ascending aorta

Palpation – Diastolic shock in aortic area.

Auscultation – Ringing 2nd aortic sound. Systolic and diastolic murmurs may be heard.

Pulse – Volume reduced. BP lower on right side.

Signs of Compression

(a) Pressure on right eparterial bronchus may cause diminished air entry at right apex.

(b) Involvement of right recurrent laryngeal nerve produces at first abductor paralysis followed by complete paralysis.

Aneurysm of arch – (Aneurysm of symptoms).

Symptoms and signs

1. **Due to compression of surrounding structures**
   - *Trachea or bronchus* – Cough, dyspnoea, haemoptysis, tracheal tug, diminished air entry in either lobe of lung and rarely bronchiectasis.
   - *Oesophagus* – Dysphagia.
   - *Vessels* – (i) Veins – Oedema of face and neck, distended neck veins, prominent veins on upper chest. (ii) Arteries – Radial pulse weaker and BP lower in left arm.
   - *Nerves*
     (a) Left recurrent laryngeal – Hoarseness of voice.
     (b) Cervical sympathetic – Horner's syndrome.
     (c) Vagus – Tachycardia.
     (d) Phrenic – Hiccough and paralysis of left dome of diaphragm.
     (e) Intercostal nerves and brachial plexus – Chest pain and pain in left arm.
     (f) *Bones* – Deep seated continuous bone pain due to erosion of bones.

2. **Systolic pulsations** – may be detected over manubrium or left interscapular region and thrill may be palpable.

V. Myocarditis – (i) *Diffuse granulomatous myocarditis* – Arrhythmias or congestive cardiac failure. (ii) *Localised gumma* – AV block or valvular pseudostenosis if gumma impinges on ventricular outflow tract.

MANAGEMENT OF CARDIOVASCULAR SYPHILIS

1. *Active treatment* – Benzathine Penicillin G 2.4 million units IM weekly for 3 weeks. Effects of Jarisch-Herxheimer reaction (fever, tachycardia) at the start of a course can be reduced by Prednisolone 30–40 mg in divided doses daily for 2–3 days before and after the first dose of antimicrobial, reducing by 5 mg/day thereafter. In case of penicillin sensitivity, Tetracycline 500 mg qds. or Doxycycline 100 mg b.d. for 4 weeks.
2. *Treatment of heart failure* – if present is carried out first.
3. *Treatment of syphilitic aneurysm* – Surgical excision of the aneurysm and replacement of excised portion by suitable graft.

9. ISCHAEMIC HEART DISEASE

ETIOLOGICAL AND RISK FACTORS

1. ***Age*** – In men and women, the mortality rate from IHD rises steeply with increasing age. It is probable that the age factor in susceptible subjects is caused primarily by the cumulative effects of multiple risk factors over time.
2. ***Sex*** – Male preponderance. After menopause however incidence in men and women is more or less same.
3. ***Body habitus*** – IHD is more common in men of endomorphic habitus – those with softness and roundness of body contour without great muscular development and with small extremities.
4. ***Ethnicity*** – Atherosclerosis and IHD can affect all races and ethnic groups, given the appropriate environment and circumstances. Migration studies show significant effects of environmental factors e.g. Japanese immigrants show the same rate of IHD as other Americans.
5. ***Serum lipids and dietary factors*** – implicated are a high intake of saturated fat and relatively low ratio of polyunsaturated to saturated fats. Intake of dietary cholesterol plays an additional but less predictable role.

   Serum cholesterol (TC) – Risk of IHD increases continuously over the whole range of serum TC concentrations.

   Serum HDL cholesterol – is regarded as the 'protective' cholesterol, low concentrations are associated with increased risk. The TC:HDL cholesterol ratio is an efficient measure of lipid-related risk.

   Serum triglycerides (TG) – Elevated levels are independent risk factor. However, TG has a role as a synergistic risk factor with other lipid risk factors.

   Small dense LDL (LDL phenotype B). LDL particles are heterogenous and have been characterised as small and large LDL. Patients with pattern B have small dense LDL. There is increased evidence linking LDL phenotype B to increased risk of IHD.

   Lipoprotein (a) [Lp (a)] – Lp (a) is an LDL particle bound to apolipoprotein B that resembles plasminogen, and this makes lipoprotein (a) play a role in both atherosclerosis and thrombosis.
6. ***Hypertension*** – carries increased risk of IHD due to degenerative effects of high pressure on arterial wall.
7. ***Cigarette smoking*** – There is a continuous increase in risk of IHD with increased intensity of cigarette smoking, particularly in younger age groups. The prevalence of IHD also seems to be appreciably increased in pipe or cigar smokers or those who chew tobacco.
8. ***Overweight and obesity*** – carry a two-fold risk of a major IHD event. Increasing body wt. is associated with increasing levels of BP, serum TC, serum TGs and serum insulin, and decreased levels of HDL cholesterol and physical activity. There is now good evidence that central obesity, as measured by the waist:hip or waist:height ratio, or even simple waist circumference, is an independent risk factor for IHD.
9. ***Physical activity*** – Studies of work and leisure activity indicate that sustained, regular physical activity in leisure time (e.g. regular brisk walking), is protective against IHD.
10. ***Diabetes mellitus*** – is not an essential cause of IHD but can aggravate the development of such disease. Asymptomatic hyperglycaemia appears to be an independent risk factor for major IHD events.
11. ***Family history*** – IHD is known to cluster in families and a positive family history of IHD, particularly if it occurs in a first-degree relative at an early age (<50 years for men, <55 for women) is an independent risk factor for IHD.
12. ***Homocysteine*** – Elevated levels of homocysteine (generally >14–15 μmol/L) are associated with increased risk of CHD. It may cause vascular damage due to its deleterious effects on endothelial function, its prothrombotic, prooxidant and mitogenic effects.
13. ***Emotional factors*** – IHD is more likely to develop in a person with aggressiveness, competitiveness and a sense of time urgency. Also in depression.

14. ***Other possible risk factors*** – Programming in foetal life due to maternal malnutrition, social inequalities involving psychosocial factors and stress, infection and inflammation (currently focussed on H. pylori and C. pneumoniae), the metabolic syndrome, thrombogenic and fibrinolytic factors, postprandial lipaemia and genetic factors.

    Major causal risk factors are – Cigarette smoking, high blood pressure, elevated serum cholesterol or LDL cholesterol, low HDL cholesterol and high plasma glucose.

ACUTE CORONARY SYNDROME (ACS)

ACS represents clinically acute myocardial ischaemia and comprises:

1. Unstable angina (UA)
2. Non-ST elevated myocardial infarction (NSTEMI)
3. ST elevated myocardial infarction (STEMI)

NSTEMI usually results from severe coronary artery narrowing, transient occlusion or microembolization of thrombus and/or atheromatous material. NSTEMI is defined as elevation of cardiac biomarkers in absence of ST elevation. The syndrome is termed unstable angina in absence of elevated cardiac enzymes.

STEMI results from complete and prolonged occlusion of an epicardial blood vessel and is defined based on ECG criteria.

Management of ACS should focus on rapid diagnosis, risk stratification and institution of therapies that restore coronary blood flow and reduce myocardial ischaemia.

ANGINA PECTORIS

Angina pectoris is the discomfort resulting from acute myocardial ischaemia.

Pathophysiology

Acute myocardial ischaemia occurs when myocardial oxygen demand exceeds supply

1. *Coronary atherosclerotic narrowing* (most cases).
2. *Non-atherosclerotic coronary artery disease* – Coronary spasm, coronary thromboembolism, congenital anomalies, coronary vasculitis.
3. *Valvular heart disease* – AS and/or AR. MS with pulmonary hypertension, mitral valve prolapse.
4. *Pulmonary hypertension.*
5. *Systemic hypertension.*
6. *Hypertrophic or dilated cardiomyopathy.*
7. *Anaemia* – from tachycardia and reduction in O_2 availability.

Myocardial viability

Myocardium that is dysfunctional but viable results from:
(1) Chronic flow impairment (*hibernating myocardium*).
(2) An episode of acute ischaemia – the duration of dysfunction depends on the severity of the ischaemic insult *(stunned myocardium).*

Precipitating Causes

1. Physical exertion
2. Heavy meal
3. Exposure to cold
4. Emotion and excitement particularly anxiety and anger
5. Hyperinsulinism in diabetic patients
6. Other causes – Straining at stool, bathing, sexual intercourse, micturition

I. Stable Angina Pectoris

Angina is said to be stable when there has been no change in the frequency, duration, precipitating factors, or ease of relief of anginal attacks during last 60 days (provided patient's activity level has not decreased during that period).

Symptoms

1. ***Typical Anginal Pain or Distress:***
    (a) *Site* – Most often over middle or lower sternum or over left precordium, at times in epigastrium. Sometimes discomfort is located only in left shoulder or left upper arm, occasionally in lower jaw, rarely in interscapular area.
    (b) *Radiation* – May spread to right or left arm or both, neck or jaw. Occasionally pain starts in the wrists, upper arms or face and then spreads to the chest.
    (c) *Character* – Vice-like constriction or choking. Sometimes only pressure or burning pain, rarely mere weakness of one or both arms. An important characteristic is its constancy, the pain being steady while it lasts.
    (d) *Duration* – most commonly 1 to 4 minutes. May force patient to stop walking.
    (e) *Provocation* – by effort specially like walking against the wind or up a climb, hurrying after meals, or unaccustomed exercise. At times due to excitement, anger, fear. In advanced cases, pain is provoked by lying down (angina decubitus) or stooping.
    (f) *Relief* – with sublingual nitroglycerine.
2. Dyspnoea – if it occurs before the pain suggests severe ventricular disease.
3. Other Symptoms – (a) Choking sensation in throat or feeling of impending doom. (b) Belching or passage of

flatus or polyuria after an attack. (c) Dizziness, faintness or rarely syncope. (d) If pain is severe, sweating and nausea.

Signs

1. *No signs.*
2. *Signs of LV dysfunction* – Atrial or third heart sound. If LV ejection time is increased, the aortic valve closes late and second sound becomes single, or splitting is reversed.
3. *Dysfunction of papillary muscle* – can lead to transient mitral regurgitation in case of ischaemia.
4. *Signs associated with risk factors* – (a) Hypertension. (b) Hyperlipidaemia–Arcus senilis, xanthelasma, or cholesterol deposits along tendons and in skin of palms and buttocks. (c) Obesity. (d) Diabetes and its accompaniments.
5. *During the attack* – Pallor and sweating with rise of BP Often tachycardia. Pressure on carotid sinus may produce slowing of pulse and cessation of pain.

Grading of Effort Angina

1. Ordinary physical activity, e.g. walking, climbing stairs does not cause angina. Angina with strenuous or rapid or prolonged exertion.
2. Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold or against a wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs in normal conditions and at normal pace.
3. Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
4. Inability to carry out any physical activity without discomfort – anginal syndrome may be present at rest.

Clinical Variations (Atypical Forms)

1. *Site and character of pain* – Pain may start in one of the sites of radiation and may be confined to that area, e.g. only the left wrist, or pain may be sharp and occur only in the left chest.
2. *Dyspnoea* – with or without angina, and exhaustion.
3. *Episodic or chronic fatigue and exhaustion* – due to reduced cardiac output secondary to ischaemia-induced depression of myocardial contractility.
4. *Second wind angina* – Pain occurs at beginning of exertion, subsequently the patient is able to 'walk off' the pain.
5. *Nocturnal angina* – may develop after a period of angina of effort, or may represent the initial pattern of angina. It may be related to dreams, or latent LV failure.
6. *Angina with syncope* – may be caused by cardiac arrhythmia.
7. *Sweating and nausea (or vomiting)* because of severe pain.
8. *Bradycardia angina* – Angina results from inability of heart to accelerate adequately in response to exercise or emotion.
9. *Paroxysmal atrial fibrillation* – may be the first evidence of ischaemic heart disease particularly in middle-aged patients.

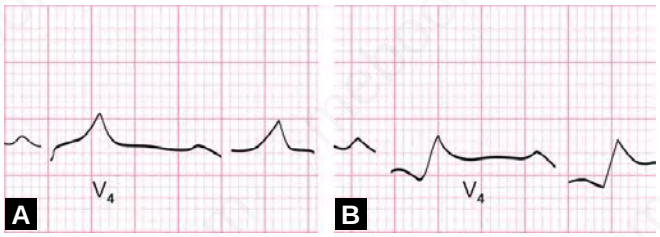
Diagnosis Tests

1. ***ECG at rest*** – may be normal or show ST-T changes suggestive of ischaemia, or AV or intraventricular conduction defects.
2. ***Holter monitoring*** – is helpful in evaluating total ischaemic burden, i.e. episodes of painful or painless myocardial ischaemia.
3. ***Stress testing*** – Cardiovascular stress can be provoked physically by exercise, or pharmacologically (in patients who cannot exercise).

   (a) Exercise stress testing – With continuous ECG monitoring and intermittent BP recording is performed with a treadmill or bicycle ergometer. Standardised protocols are used (e.g. Bruce protocol), enabling performance to be assessed in same patient at different times and work-load at onset of symptoms or ECG changes to be determined. An exercise ECG is abnormal if there is horizontal or down-sloping ST segment depression of 0.1 mm or more in any lead (Figs. 99A and B).

   (b) Pharmacological stress – (Myocardial perfusion scintigraphy) – Use of isotope labelled perfusion tracers and scintigraphic imaging to demonstrate areas of reduced myocardial perfusion is a sensitive and reliable method of establishing a diagnosis of myocardial ischaemia – vasodilator stress with dipyridamole or adenosine, as well as catecholamine stimulation with dobutamine or arbutamine.

   The isotope cardiovascular stress (usually thallium-201 or technetium-99 m) is injected at peak exercise and images taken with a camera immediately or shortly after exercise and compared with rest images taken a few hours later following a sec-



Figs. 99A and B: Positive exercise test. A. Control tracing before exercise within normal limits. B. Striking ST depression after exercise

ond injection of tracer. Areas of myocardial ischaemia are identified by reduced isotopic uptake in the same anatomical distribution stress images but not resting images (reversible defect).

Indications – (i) Patient unable to exercise or with limited capacity to exercise. (ii) Patient with resting or exercise-induced LBBB.

4. ***Coronary angiography*** – remains the 'gold standard' technique for diagnosis and planning treatment of IHD (Fig. 100).

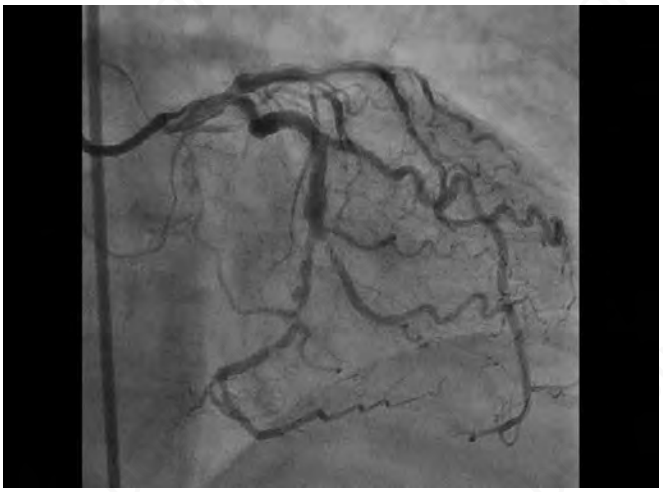


Fig. 100: Coronary angiography showing multivessel disease

Differential Diagnosis

See D.D. of myocardial infarction.

Anxiety states – (Table 64)

Table 64: Differentiating anxiety from angina

Angina pectoris	*Anxiety states*
Usually in men over 50	Common in women and young men.
Pain sternal or across chest.	Pain mammary, above or below left breast.
Radiation to one or both arms, neck and jaw.	Radiation to left scapula, left arm and left side of neck.
Sensation of constriction, tightness, or pressure.	Dull ache or soreness with stabbing or shooting pain.
Provoked by effort.	Provoked by worry and fatigue.
Pain during effort.	Pain may occur after effort.
Relieved at once by halting.	May persist for hour or day, little and slow relief by rest.
Usually well apart from pain.	Symptoms of general and neurotic ill-health. Sighing respirations.

Investigations

Echocardiography – 2D and M-mode echocardiography are valuable in assessment of resting ventricular function and can identify areas of segmentally reduced contraction corresponding to previous MI.

Stress echocardiography – Continuous 2D-echocardiography is performed at rest and during and after stress and image comparison is used to determine the extent and distribution of wall motion abnormalities.

Stress can be provoked by exercise or by pharmacological stimulation which can be used to predict the location and severity of underlying coronary artery disease.

Intravascular ultrasonography (IVUS) – defines completely the vessel wall, plaque burden, morphology of the plaque, presence of calcification in the lesion, and luminal dimensions.

Intracoronary Doppler – Clinical applications include assessment of functional significance of intermediate lesions by coronary arteriography. With use of Doppler wire the velocities and coronary flow reserve across the lesion can be estimated.

Management

I. ***Acute attack*** – Glyceryl trinitrate 0.6 mg or isosorbide dinitrate 5 mg sublingually, or nitrite spray in a measured dose of 0.4 mg. Effect starts in 3 to 5 minutes and its action lasts for 20 to 40 minutes. Contraindicated in patients with glaucoma.

II. ***Prophylaxis*** – In chronic stable angina.

General measures

1. *Control of risk factors* – (a) Hypertension. (b) Cigarette smoking. (c) Hyperlipidaemia. (d) Obesity. (e) Correction of disorders which increase myocardial oxygen demand such as anaemia and hyperthyroidism if present.

2. *Rest and exercise* – Bed rest not essential unless frequent attacks. Moderate exercise which does not cause pain or dyspnoea allowed.
3. *Relaxation techniques* and stress management.
4. *Aspirin* – 75–150 mg/day.
5. *Sedatives* – to relieve mental tension and control emotional factors.

Antianginal agents

See Table 65 for the antianginal agents.

Symptom deterioration – Symptoms may worsen because of worsening in underlying condition, development of tolerance or poor patient compliance. Further investigation is then indicated, specifically angiography with a view to revascularization by angioplasty or surgery.

Myocardial Revascularization Techniques

Percutaneous transluminal coronary angioplasty (PTCA)

Indications

1. **Chronic stable angina:**
   (a) *Single vessel disease* – Diameter stenosis of >70% in an epicardial coronary artery that supplies a large area of viable myocardium with evidence of myocardial ischaemia by low level of exercise. (i) Prior cardiac arrest of sustained VT in absence of acute MI. (ii) Must undergo high risk noncardiac surgery with objective evidence of ischaemia. (iii) Symptomatic despite medical therapy or intolerant to medical therapy.
      1. Unstable angina/acute coronary syndrome
      2. In presence of myocardial infarction
      3. Angina after myocardial infarction
      4. After bypass surgery when surgical grafts get narrowed or new lesions form in native coronary arteries.
      5. In patients who are at high risk for CABG, e.g. elderly, kidney failure, emphysema.
      6. Multivessel disease in patients who do not wish for a surgical procedure.
2. **Acute myocardial infarction:**
   (a) *Primary PTCA* – Direct angioplasty without thrombolytic therapy for evolving MI results in better arterial patency compared to lytics, with improved survival and reduced recurrent ischaemia. Indications – (i) Thrombolytic therapy contraindicated. (ii) Acute MI with cardiogenic shock.

Table 65: Antianginal agents

Drug	*Dose*	*Side-effects*
Nitrates		
Glyceryl trinitrate	0.3-0.6 mg sublingual	Headache
Transdermal	5–10 mg/24 hrs.	Headache in early stages
Isosorbide dinitrate	30–120 mg in divided doses	
Isosorbide mononitrate	40–100 mg in divided doses	
β-blockers		
Non-selective		
Propranolol	30–360 mg in divided doses	Bronchospasm. Bradycardia
Nadolol		Cold peripheries
Pindolol		
Selective		
Metoprolol	50–200 mg/day	Bronchospasm
Atenolol	50–100 mg/day	Bradycardia. Cold peripheries
Bisoprolol	10–20 mg/day	Postural hypotension
Nebivolol	5–10 mg/day	
Calcium channel blockers		
Verapamil	40–120 mg. t.d.s.	Conduction disturbance
Nifedipine	10–20 mg t.d.s.	Flushing, headache,
Amlodipine	5–10 mg/day	peripheral oedema
Diltiazem	30–60 mg t.d.s.	
Potassium-channel activator		
Nicorandil	10-20 mg t.d.s.	Headache. Hypotension
Cytoprotective effects		
Trimetazidine	20 mg t.d.s.	Gastric discomfort, nausea, headache
Inhibition of SA node		
Ivabradine	5 mg b.d.	Nil. No negative inotropic effects

   (b) *Rescue (salvage) PTCA* – Emergency angiography in acute MI with ongoing chest pain and hemodynamic problems or in asymptomatic patients with anterior MI and persistent or increasing ST elevation 90 min. after thrombolytic therapy. PTCA is then performed on high grade culprit lesion with impaired flow, or occluded artery.

(c) *Delayed PTCA* – in asymptomatic patients following successful reperfusion with thrombolytic therapy. However no difference has been shown in mortality, reinfarction or ejection fractions as compared to successful thrombolysis. Any asymptomatic patient following thrombolysis should undergo noninvasive evaluation including echocardiography and stress testing.

(d) *PTCA for post-MI ischaemia* – Post-infarction angina is an absolute indication for angiography and revascularization.

Interventional Devices

Intracoronary stents – scaffold the arterial wall and maintain stretch of a diseased segment of artery. Uses – (a) Prevention of restenosis. (b) Treating abrupt closure or threatened closure. (c) Improving an inadequate angiographic result during PTCA. The risk of closure can be minimised by use of. Absorb Bio-reabsorbable Vascular Scaffold (BVS). It functions similar to a metallic stent in the initial phase and then dissolves overtime allowing vessel to return to its natural state, other benefits are elimination of sources of vessel inflammation and provide option for future interventions unobstructed by a permanent implant. Drug eluting stents (DES) are used to avoid risk of stenosis.

Coronary atherectomy – refers to removal of atheromatous material from the coronary lesions. (a) Directional and rotational atherectomy physically cut the atheroma. (b) Rotablation abrades and pulverises the plaque. (c) Transluminal extraction atherectomy (TEC) is used for aspirating plaque and thrombus cut by the rotating blade.

Coronary artery bypass graft (CABG) surgery: Indications – (a) Patients who fail to respond to medical therapy or are incapacitated by pain. (b) Those in whom anginal attacks are accompanied by major complications e.g. ventricular tachycardia. (c) Patients with stenosis of left main coronary artery or of all three major vessels.

(a) *Saphenous vein grafts* – Disadvantage is the high percentage of significant attrition rate with atherosclerotic changes after some time (Figs. 101 and 102).

(b) *Arterial revascularization* – The internal mammary artery is used as a conduit of choice for left anterior descending artery because of its superior patency rates. Other arterial conduits used include right internal mammary artery, gastroepiploic artery, the free radial artery.

Minimally invasive coronary artery surgery *(MICAS)* – attempts to avoid the use of cardiopulmonary bypass. In patient with single vessel disease, through a midsternotomy or small anterior thorax incision, the internal mammary artery is anastomosed to the coronary artery, most commonly the left IMA to left anterior descending artery, so that blood can be diverted round the blockage. Esmolol is used to reduce heart rate and contractility, thus facilitating performance of anastomosis without going on cardiopulmonary bypass.

Transmyocardial revascularization: With the help of CO_2 laser. For patients unsuitable for CABG or angioplasty procedures, such as high risk group either with extensive, long standing multivessel disease or associated with severe uncontrollable diabetes, or kidney failure, or even patients with multiple and failed CABGs.

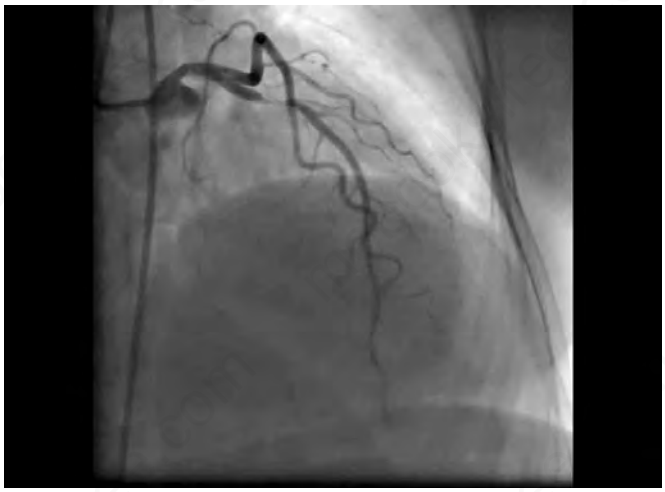


Fig. 101: Coronary angiography showing single vessel disease

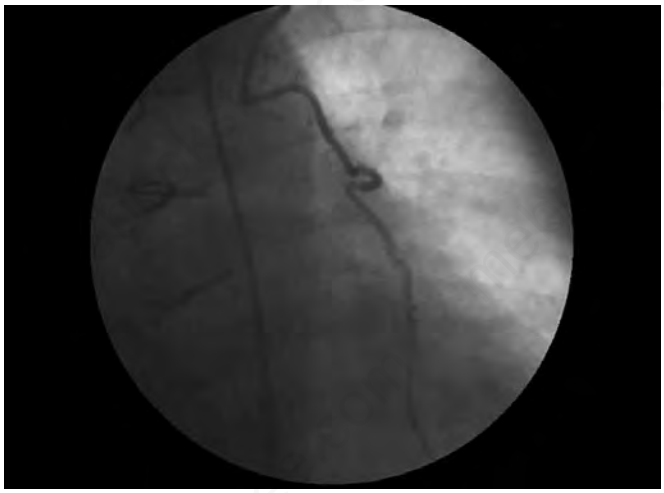


Fig. 102: Angiography after coronary bypass graft

Variant (Prinzmetal's) angina-*Diagnostic criteria:*

- Anginal attacks occur at rest.
- Attacks often worse in morning.
- ECG – shows transient ST elevation instead of depression during chest pain or Holter monitoring.

Pathogenesis: Coronary vasospasm accounts for episodes. Majority of patients have associated atherosclerotic coronary artery disease.

Diagnostic Tests

1. *ECG* – during episode of chest discomfort. Besides ST segment elevation, transient abnormal Q waves, AV heart block, ventricular arrhythmias may be detected.
2. *Coronary angiography.*

Management

1. Drugs – Nitrates and calcium antagonists. Beta blockers may exacerbate.
2. Avoidance of exposure to cold environments.
3. Tobacco smoking to be discontinued.
4. Coronary bypass surgery if coronary stenosis.
5. Angioplasty – in selected patients if significant obstruction in one coronary artery. Possibility of angioplasty-induced coronary spasm.

II. Unstable Angina (UA/NSTEMI)

Diagnostic criteria of unstable angina:
See Table 66.

Pathogenesis: In unstable angina, myocardial ischaemia results from a primary decrease in oxygen delivery rather than in increase in myocardial oxygen demand.

Statins and other drugs are recommended for all NSTE ACS patients irrespective of cholesterol level with the aim of achieving LDLC levels <70 mg/dL. ACE inhibitor in patients with reduced LV systolic function. ARBs in those who are intolerant.

Table 66: Diagnostic criteria of unstable angina

• Angina on effort of recent onset (one month).
• Angina of effort with increasing frequency and duration and provoked by less than usual stimuli (accelerated or crescendo angina).
• Prolonged (>20 min) anginal pain at rest
• Angina in early (<1 month) post-infarction period.
• New onset (de novo) severe angina,
• Recent destabilization of previously stable angina with crescendo angina
• Post MI angina

Coronary revascularization to relieve angina, ongoing myocardial ischaemia and progression to MI or death.

Indications

Refractory angina (e.g. evolving MI)

- Refractory angina despite intense antianginal treatment (associated with ST segment depression (<2 mm) or deep negative T waves
- Clinical symptoms of heart failure or hemodynamic instability (shock)
- Life-threatening arrhythmia (VF or VT)

Conservative and Invasive Strategy

High risk/unstable patients benefit most from early revascularization. The mode of revascularization is usually based on the severity and distribution of CAD. CPI usually performed for the culprit lesion using Bioresorbable vascular scaffold (stent). CAG is advised for complex CAD not amenable to PCI, left main with triple vessel disease, total occlusions and diffuse disease.

Long-term Management

Patients with NSTE ACS after initial phase carry a high risk of recurrence of ischaemic events. Therefore, active secondary prevention is an essential element of long-term management.

III. Acute ST Segment Elevation Myocardial Infarction (STEMI)

Precipitating Factors:

- Physical exertion–Attack more often during physical effort than at rest, unaccustomed effort may precipitate attack.
- Emotional strain acute or prolonged.
- Heavy meal.
- Sudden fall of blood pressure, e.g. shock, post-operative or anaesthesia.

Symptoms

Premonitory – Patient may or may not give history of prior angina pectoris.

Clinical presentation of NSTEMI ACS is retrosternal pressure or heaviness radiating to left arm, neck or jaw which may be intermittent (usually lasting several minutes) or persistent. There are several atypical symptoms such as epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with pleuritic symptoms or increasing dyspnoea. It is important to identify clinical circumstances that may precipitate or exacerbate such as anaemia, infection, fever and metabolic or thyroid disorders.

1. **ECG** may show ST segment deviation, T wave changes or may remain normal, ST segment shift and T wave changes are indicators of unstable angina. ST depression >2 mm carries and increased mortality risk. Inverted T waves, especially of ≥2 mm (0.2 mv) also indicate UA/NSTEMI. Q waves suggesting prior MI indicate a high likelihood of IHD.
2. **Echocardiography** and Doppler examination should be done after hospitalization to assess global LV function. ECHO also helps in excluding other causes of chest pain.

Management of NSTEMI

1. Approach

- Patients who are awaiting hospitalization are advised to chew non-enteric coated Aspirin3 25 mg and use sublingual nitrate to relieve pain.
- High-risk patient should be hospitalized in CCU and observed for at least 24–48 hours.
- Fibrinolytic (thrombolytic) therapy should not be used in patients with UA or NSTEMI because they can prove harmful. Glycoprotein IIb/IIIa agents like abciximab, tirofiban and eptifibatide are mostly useful in patients undergoing percutaneous coronary intervention (PCI).

Anti-ischaemic and analgesic therapy

- O_2 for initial stabilization particularly those with hypoxaemia.
- Nitrates - Topical, oral or IV for pain relief. IV nitroglycerine is particularly helpful in those unresponsive to sublingual NTG, in hypertension and those with heart failure. Nitrates should be used with caution if systolic BP is below 100 mm Hg.
- Oral beta blockers are useful for pain relief.

2. Antiplatelet agents.

Aspirin - Initial dose of chewed non-enteric Aspirin is 162–325 mg, subsequent dose can be 75–100 mg/d on long-term basis.

- Clopidogrel in all patients with immediate dose of 300 mg followed by 75 mg/d. In patients considered for PCI, a loading dose of 600 mg is advised to achieve more rapid inhibition of platelet function. It should be given for at least 12 months unless there is excessive risk of bleeding, or Prasugrel. 60 mg as single dose initially maintenance 5–10 mg/day.

Anticoagulants include unfractionated heparin: Low molecular wt. heparin, fondaparinux and bivalirudin. (a) Enoxaparin 1 mg/kg body wt. twice daily is preferred in patients treated conservatively or by invasive strategy. (b) Fondaparinux is recommended on basis of favourable efficacy/safety profile. Dose 2.5 mg/d. (c) Bivalirudin is recommended for urgent and elective PCI in moderate or high-risk patients. It needs bolus of heparin additionally during PCI to prevent stent thrombosis.

Symptoms: Patients may experience a range of symptoms varying from crushing retrosternal or left-sided chest pain discomfort, with associated typical symptoms to isolated dyspnoea, syncopal attacks, malaise and breathlessness. Elderly diabetic and patients on NSAIDs may suffer silent MI. These patients are commonly found to have cardiogenic shock, hypotension, arrhythmias and conduction blocks and acute LVF.

Characteristic associated with adverse outcomes

1. Older age (>75 years)
2. Systolic BP <150 mm Hg
3. Heart rate >100/min
4. Anterior MI

Investigations

1. **ECG**

   Progression of ECG Changes

   (a) T wave abnormalities: Symmetrically tall T waves or inverted T waves of ischaemia.

   (b) ST segment elevation in leads overlying area of infarction.

   (c) ST elevation with T inversion.

   (d) Evolution of pathological Q waves, suggesting cell death.

   Diagnosing infarction in presence of LBBB: ST segment elevation with tall positive T waves is seen frequently in right precordial leads with uncomplicated LBBB. Secondary T wave inversions are present in lateral precordial leads. However appearance of ST segment elevation in lateral leads suggests IHD (specificity 92%). ST segment depression and/or deep T wave inversion in leads to V_1 to V_3 also suggests underlying ischaemia.

Localization of infarct by ECG

See Table 67 for the localization of infarct from ECG (Fig. 103).

Table 67: Localization of infarct from ECG

Area of infarct	*Leads showing abnormal Q waves*
Diaphragmatic	II, III, aVF
Antero-lateral	I, aVL, V_5, V_6
Antero-septal	V_1, V_2, V_3, V_4
True posterior	Tall R in V_1, V_2
Right ventricular	Tall R in V_3R, V_4R

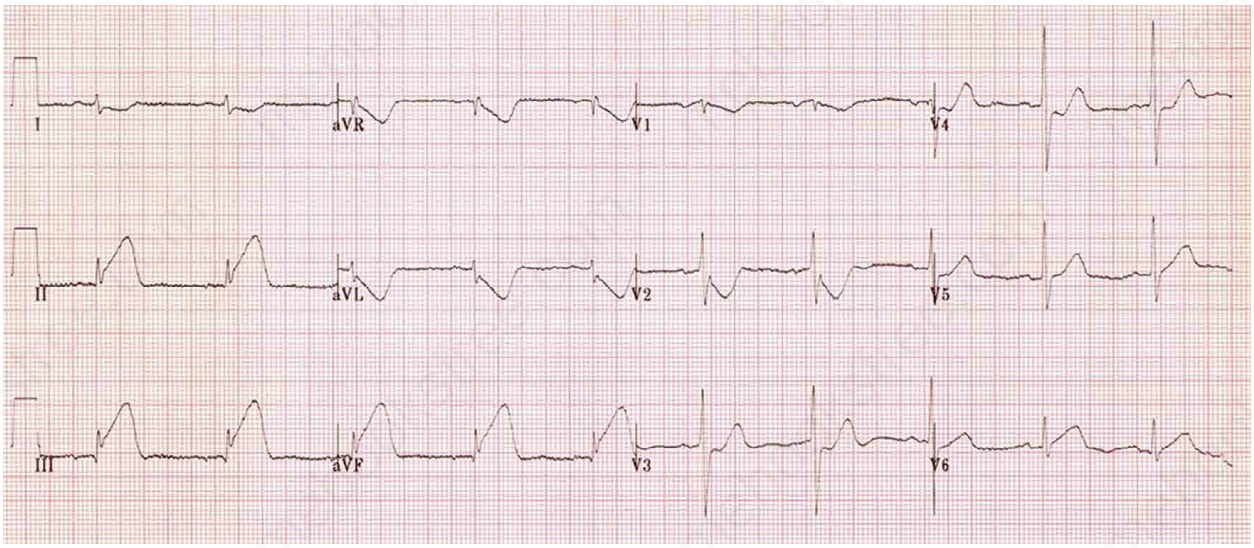


Fig. 103: 12-lead ECG showing acute inferior wall myocardial infarction

2. **Raised biomarkers**
   Common biomarker
   (a) *Myoglobin* is first to rise with myocardial necrosis but its specificity is less, therefore, seldom used.
   (b) *Creatine kinase isoenzymes.* Cardiac muscle mainly contains both MM and MB isoenzymes. The CPK-MB combination is used for diagnosing MI in acute coronary syndrome.
   (c) *Cardiac specific troponins* I and T are now considered the preferred biomarker for diagnosing MI. Other causes of raised troponins are injury to cardiac muscle, e.g. cardiac catheterization, shock, cardiac surgery. While CK-MB increases 10 to 20 fold above upper limits of reference range, CTnT and CTn1 increase more than 20 times. Hence how troponins are specific and sensitive markers for acute MI. CKMB is useful now for diagnosis re-infarctions remain elevated for a longer time.

   See Table 68 for the summary of cardiac biomarkers.

   (d) *Heart type fatty acid binding protein (H-FABP)* has been shown to be a sensitive early marker of myocardial infarction. Cut-off value is <5.48 µg/L. Troponin negative patients with FABP >6.48 µg/L represent a very high-risk group of patients.
3. ***Radionuclide imaging*:**
   (a) *Thallium-201 imaging* – Areas of infarction appear as fixed defects in resting perfusion scans.
   (b) *Technetium-99m labelled pyrophosphate* – Scans do not become positive until after 12–24 hours which is not ideal. The technique is useful in patients with LBBB or who are permanently paced (because in these cases ECG does not show changes of ischaemia or infarct, these being masked), or where results of enzyme tests are equivocal.
4. ***Echocardiography*** – can identify akinetic and hypokinetic regions caused by infarction but cannot discriminate accurately between old and new infarcts.
5. **MRI** – MRI with contrast (gadolinium) can diagnose MI accurately, showing late enhancement in infarcted zone.

Table 68: Cardiac biomarkers in AMI

Biomarker	*Initial elevation*	*Peak elevation*	*Return to normal*
Myoglobin	1–4	6–7 hr	24 hr
MB-CK	3–12	24 hr	48–72 hr
CTn1	3–12	24 hr	5–10 days
CTnT	3–12	12 hr–2 days	5–14 days

Differential Diagnosis (of precordial pain):

I. Ischaemic Cardiac Pain

1. ***Angina pectoris*** (Table 69)
2. ***Cardiac arrhythmias*** – Sudden onset of arrhythmia with tachycardia may be associated with oppressive substernal pain which may be prolonged, and with sweating and dyspnoea.
3. ***Mitral valve prolapse*** – Chest pain not related to exertion, usually sharp over precordium, commoner in those with anxiety or nervous temperament. Mid-systolic click with late systolic murmur.

Table 69: Dfferentiating myocardial infarction from angina

		Angina pectoris	*Myocardial infarction*
1.	Exciting factors	After exertion, cold or heavy meals	Without visible cause, usually during rest at night
2.	Attitude	Immobile	Restless
3.	Pain		
	Site	Retrosternal	Usually retrosternal but may be precordial
	Duration	Never more than 5 minutes	About half an hour or more
	Radiation	To both arms, neck or jaw	Not so diffuse
	Relief	Nitrites	Nitrites have no effect
4.	Vomiting	Absent	Common
5.	Dyspnoea	None. Only breath held	Common
6.	Shock	Absent	Marked
7.	Sweating	Slight	Profuse
8.	Fever	Absent	Present
9.	Heart sounds	Normal	Weak, gallop rhythm
10.	Pericarditis	Absent	May occur
11.	Pulse	Normal or rapid	Small, rapid, often irregular
12.	B.P.	Normal or increased	Tendency to fall
13.	Cardiac failure	Absent	Occurs early
14.	Cardiac enzymes	Normal	Raised
15.	ECG	Transitory change during attack	Progressive, typical changes

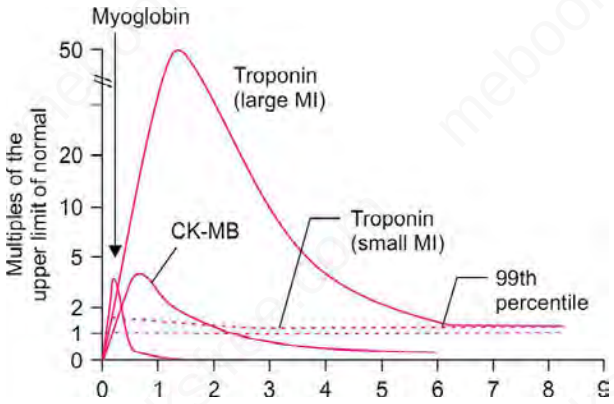


Fig. 104: Time profile and limit of rise of cardiac biomarkers after acute myocardial infarction

Table 70: Differentiating myocardial infarction from aortic dissection

	Aortic dissection	*Myocardial infarction*
Fainting	Common	Uncommon
Pain	Chest or back, transmitted to both arms or legs or back. Peak intensity at onset	Precordial or epigastric, transmitted to left arm. Increases in intensity after it commences
Nervous symptoms	Possible paralysis	Nil
Murmur	Aortic diastolic murmur may appear	Apical systolic murmur may be heard
BP	Usually remains high	May fall
Other arteries	May show signs of involvement	Not affected
ECG	Normal or changes consistent with pericarditis	Typical pathognomonic changes
Chest X-ray	Widening of supra-cardiac shadow. Double aortic knob may be seen.	No specific abnormality
Serum enzymes	No change	Elevated

II. **Affection of aorta**

1. ***Aortitis*** – Uncomplicated syphilitic aortitis may be accompanied by substernal pain. The pain is localised and not influenced by exertion.
2. ***Aortic dissection*** (Table 70)

III. **Pericarditis** (Table 71)

IV. **Pulmonary disease**

1. ***Massive pulmonary embolism*** (Table 72)
2. ***Spontaneous pneumothorax on left side*** – Pain is usually sharper and more localised to side of chest than to sternal region. Initial spontaneous pain more transient with subsequent pain intensified with deep inspiration or change of posture. Dyspnoea only with effort, hyper-resonance, diminished or absent breath sounds over affected part and sometimes shift of mediastinum. Chest radiograph diagnostic.
3. ***Acute pleurisy*** – Pain aggravated by deep inspiration and usually in axillary region. Pleural rub.
4. ***Pneumonia*** – If in a case of coronary occlusion there is little pain but prominent dyspnoea, fever and rales over circumscribed area of lung, pneumonia may be diagnosed. In pneumonia pain inside of chest aggravated by deep breathing. High fever and leucocytosis.

Table 71: Differentiating myocardial infarction from acute pericarditis

	Viral pericarditis	*Myocardial infarction*
Pain	Increased by deep breathing or lying flat or coughing. Pain radiating to trapezius.	Not affected by postural change or cough
Friction rub	Within first few hours	24–48 hours after onset of pain
Serum enzymes	Usually no change	Elevated
ECG	Raised ST segments in all three limb leads with concavity upwards No abnormal Q waves.	Reciprocal elevation and depression of RS-T in I and III, prominent Q_1 or Q_3

V. **Mediastinal conditions**

1. ***Acute mediastinal emphysema*** – Severe substernal pressure which may radiate to back, neck, shoulders and rarely arms. Shock rare. Loud, bizarre, crunching sounds over sternum and precordium coinciding with cardiac systole. Variation in pain with change of position. Associated subcutaneous emphysema. X-ray – Air in pleural cavity and anterior mediastinum.
2. ***Acute mediastinitis*** – May be associated with severe substernal pain. Clinical manifestations of primary disease, e.g. injuries to chest wall or inflammatory process in lungs, pleura, or sternum. Fine crackles over sternum on deep breathing or synchronously with heart beats.

VI. **Gastrointestinal affections**

1. ***Acute indigestion*** – Pain not typically retrosternal and no radiation. Shock absent. Marked dyspeptic symptoms. ECG - Normal.
2. ***Acute cholecystitis and cholelithiasis*** – Pain colicky in nature. Usually in epigastrium at onset. Radiation to back beneath right scapula or shoulder. An early sign may be a palpable distended gall bladder (Cope's sign). The GB may then expel its contents and both pain and swelling may disappear for few hours followed by localisation of pain in right hypochondrium. No dyspnoea. Jaundice may be present. History of previous attacks.
3. ***Acute abdomen*** – e.g. perforated ulcer (Table 73).
4. ***Oesophageal chest pain*** – (Oesophageal spasm, 'oesophageal colic') – Unpleasant, often severe, dull or gripping pain in central chest, often radiating to back, epigastrium, throat and sometimes, to shoulders and upper arms. Lasts from few seconds to several minutes, and if prolonged, may be associated with vasovagal effects. History of dysphagia, heartburn, and persistence of a dull ache that lasts for hours to days after a more severe episode. Causes –

   (a) *Diffuse spasm and achalasia* – It can be precipitated by injection of methacholine or ergometrine.

Table 72: Differentiating myocardial infarction from acute pulmonary embolism

	Pulmonary embolism	*Myocardial infarction*
History	Convalescent	Of angina on effort
Pain	Severe, usually central chest pain	Pressing or crushing substernal, radiating to shoulder or arm
Shock	Frequently first symptom	Usually after several hours of increasing pain
Gallop	Adjacent to sternum, increased by insp.	Apical, louder during exp.
Cough	Severe	Rare
Cyanosis	May be marked	Mild or none
Haemoptysis	May occur later	None
Fever	Early, may reach high level	24–36 hours after onset, moderate
JVP	Raised	Normal
Heart sounds	Loud pulmonary 2nd sound and systolic murmur (of TR)	Feeble heart sounds or gallop rhythm
X-ray	Pulmonary infarction	Not characteristic
ECG	Right axis deviation, right atrial P waves, RBBB	Typical according to location of infarction

Table 73: Differentiating myocardial infarction from acute pulmonary embolism

Acute abdomen	*Myocardial infarction*
History of abdominal symptoms	History of angina
Radiation of pain over abdomen	Radiation of pain to arms
Pulse may be slow at onset	Pulse rapid
Respiration shallow and thoracic	Respiration abdominal
Rigidity external and persists	Rigidity not so board like and varies with respiration
Heart sounds normal	Diastolic gallop

(b) *Symptomatic oesophageal peristalsis* ('nut-cracker oesophagus') – Intermittent severe chest pain resembling cardiac pain. Manometric studies will show pressure generated by peristaltic wave grossly abnormal (over 160 mm Hg).

(c) *Reflux oesophagitis* – Some patients experience severe pain of 'spasm', superimposed on recurrent heart burn, or sole symptom of reflux and revealed by appropriate investigations.

(d) *Ruptured oesophagus* – Severe pain in centre of chest radiating to back. Usually follows attempts to suppress vomiting. In MI, pain precedes vomiting.

5. ***Hiatus hernia*** – Pain usually simulates angina but if persisting over an hour resembles coronary occlusion. Both sexes equally affected. Fullness during or shortly after meals, regurgitation, belching, nausea and vomiting common. Pain at night can be prevented by sleeping propped up on pillows, aggravated by stooping or bending forward. Pain commonly burning and relieved by antacids.
6. ***Acute pancreatitis*** – May be associated with acute onset of substernal oppression as well as epigastric pain. Diagnosis made by presence of elevated blood amylase, and signs of upper abdominal peritoneal irritation.
7. ***Internal haemorrhage*** – May present as a syndrome of prolonged, sudden, severe anginal pain, shock and collapse and even ECG may show changes since the coronaries participate in the general vasoconstriction.

VII. **Lesions of muscular system** – Skeletal muscles usually involved are pectoralis and serratus anterior. Presence of trigger areas, rheumatic tendency of patient and finding of painful motion elsewhere in the body.

VIII. **Neurovascular affections** –

1. ***Nerve root pain*** – Due to skeletal lesions such as cervical disc, spondylitis; osteoarthritis, shoulder arthritis, cervical rib. Pain not related to effort, but often related to movement of neck, shoulder, arm, coughing or sneezing. Objective neurological signs may be present and local tenderness can generally be elicited.
2. ***Herpes zoster*** – Chest pain may precede the eruption by three days. Pain burning or shooting in character and often associated with hyperalgesia of the area of skin supplied by the affected nerve root.

IX. **Cardiac neurosis and neurocirculatory asthenia** – Dyspnoea in form of inability to take deep breath. Excessive tendency to sigh. Pain dull or sharp, continuous or intermittent usually in region of apex. Associated local tenderness. Palpitation and fatigability common.

X. **Vasomotor and endocrine disorders**

1. *Ovarian dysfunction (Menopause)* – Pain in cardiac area, palpitation, dyspnoea and hot flushes. Pain usually not substernal and not provoked by exertion or excitement. May last for hours. Area of tenderness on 4th or rarely 5th rib to left of sternum at costochondral junction. Infiltration with novocaine affords relief. Vertigo and paraesthesias common.
2. *Hypertensive crisis of phaeochromocytoma* – Palpitation, sweating, dizziness and pain. Pain anginal and may radiate to both arms. Severe headache and epigastric pain common. Marked rise of B.P. Increased urinary excretion of catecholamines and VMA.

Complications and Their Management:

A. Mechanical

1. **LV failure and cardiogenic shock** – Haemodynamic monitoring with an arterial line and pulmonary artery catheter is helpful. 2D-Echo determines the extent of myocardial involvement and other complications of AMI which contribute to cardiogenic shock.

   In patients with cardiogenic shock an intra-aortic balloon pump (IABP) insertion reduces the afterload and improves cardiac output and decreases myocardial O_2 requirement. Temporary Left Ventricular Assist Device (LVAD) allows time for recovery of stunned or hibernating myocardium. Inotropic and vasopressor agents may be given at lowest possible doses. Survival improvement is associated only with PCI or CABG.
2. **RVMI** – As RV has lower O_2 requirement and is thin walled, is perfused during systole and diastole. RVMI rarely causes irreversible damage. Management – Volume loading to increase preload and CO. If volume loading fails to increase CO, inotropes may be added. Reperfusion improves RV function and decreases mortality rates. Tricuspid valve replacement or repair if severe TR.
3. **Ventricular Septal Rupture (VSR)** – Normally occurs 2–4 days after MI, a new pansystolic murmur develops especially associated with biventricular dysfunction. 2D Echo with colour flow imaging is the test of choice. Percutaneous closure with paediatric VSD occluder

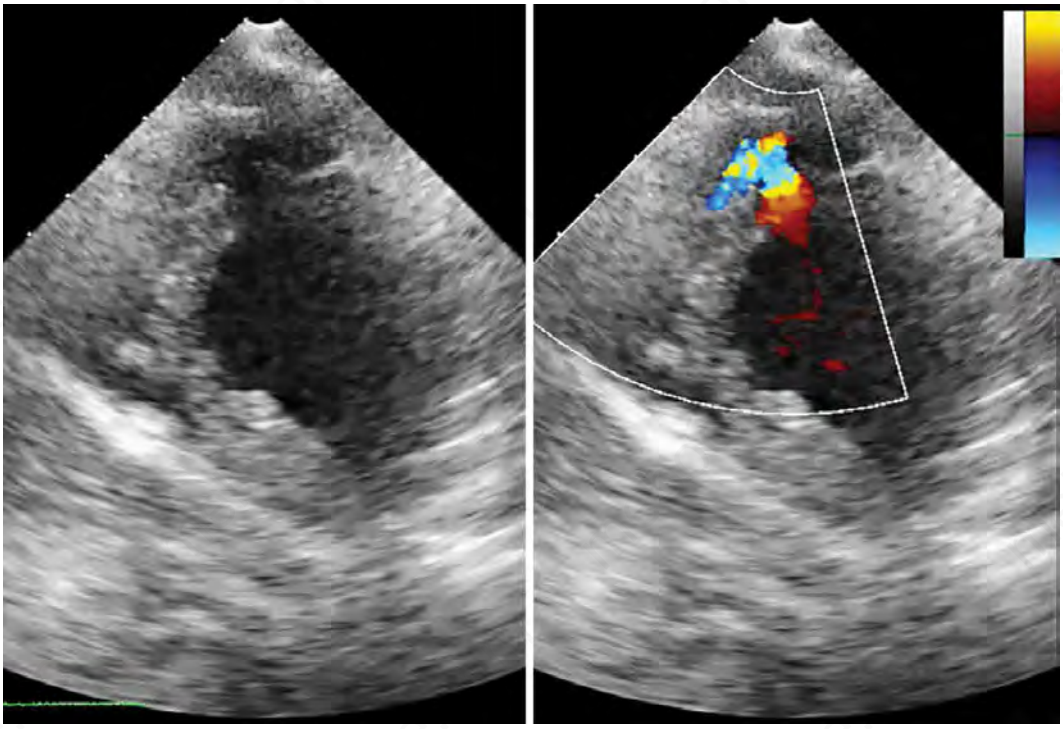


Fig. 105: Ventricular septal defect after myocardial infarction

device may be useful for high-risk surgical patients (Fig. 105).

4. **Mitral regurgitation** – Severe or acute MR caused by papillary muscle dysfunction is a life-threatening complication. Vasodilator therapy is useful as it reduces SVR and increases CO. Surgical therapy: CABG + mitral valve replacement should be considered immediately. Patients with moderate MR may do well with mitral valve repair.
5. **Cardiac free wall rupture** (FWR) – Occurs in first 5 days in 50% and within 2 weeks in 90% of patients. With acute rupture there is electromechanical dissociation and sudden death. In subacute rupture patients have distended jugular veins, pulsus paradoxus, diminished heart sounds and pericardial rub. 2D-Echo reveals cardiac tamponade – RA systolic collapse, dilated IVC and marked respiratory variation in mitral and tricuspid inflow. *Treatment* – Immediate pericardiocentesis. Emergency thoracotomy with surgical repair is definitive therapy.
6. **Pseudoaneurysm** is caused by a contained rupture of the LV free wall. The outer wall is formed by the pericardium and mural thrombus. Pseudoaneurysms communicate with the body of LV through a narrow neck. Chest X-ray may show cardiomegaly with an abnormal bulge on cardiac border. 2D-echo, MRI, CT-scan may help confirm the diagnosis. Surgical resection is advised regardless of the size of the pseudoaneurysm.
7. **True ventricular aneurysm** – Can be acute or chronic. Acute development of a large LV aneurysm can result in CHF and even cardiogenic shock. They usually occur in transmural MI involving apex of the LV. When chronic aneurysms (Figs. 106 and 107) persists for more than 6 weeks after MI, patients may have heart failure, ventricular arrhythmias and systemic embolism due to LV clot (Fig. 108) but may be asymptomatic. ECG shows persistent ST elevation. 2D-Echo helps to differentiate true aneurysm which has a wide neck, where as a pseudoaneurysm has a narrow neck. *Management*. Heart failure with acute aneurysm – IV vasodilators, an IABP, with chronic aneurysms – ACE inhibitors, digoxin and diuretics. Anticoagulation with warfarin is indicated for patients with a mural thrombus with INR of 2 to 3 for 3 to 6 months. PCI has beneficial effects on LV remodelling. ICD is indicated in patients with intractable ventricular arrhythmias refractory to medications. Those with refractory heart failure and refractory ventricular arrhythmias should be considered for surgical resection (Dorr's procedure). Revascularization is beneficial to patients with a large amount of viable myocardium in the aneurysmal segment.

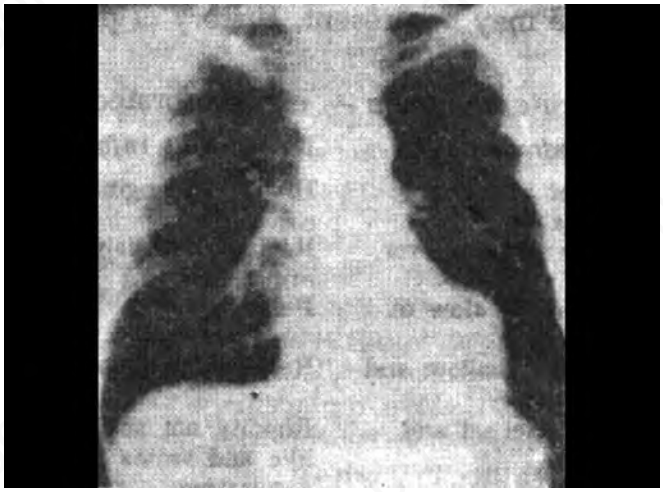


Fig. 106: Left ventricular aneurysm. A bulge on the left heart border may also be due to pericardial cyst, pericardial sac defect, myocardial mass (neoplasm, hydatid), or coronary artery aneurysm or left atrial appendage

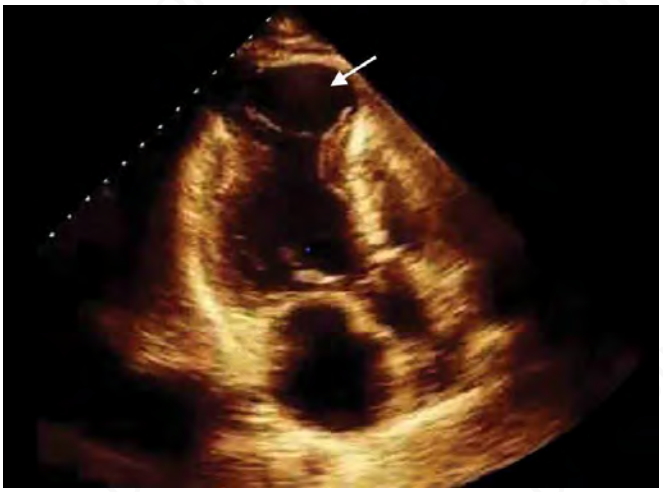


Fig. 107: Left ventricular aneurysm

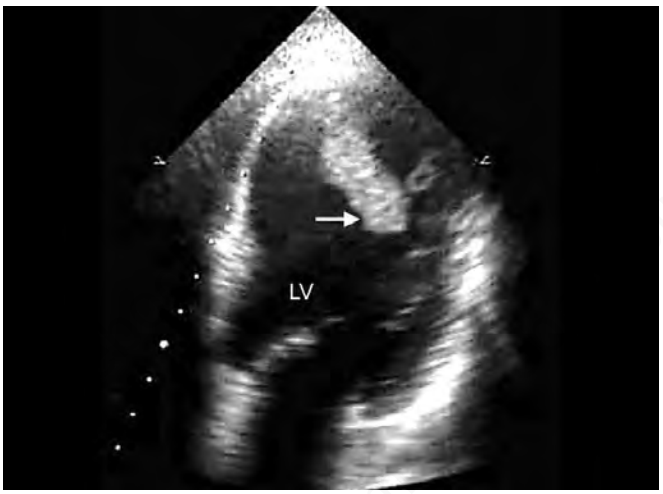


Fig. 108: 2D echo showing thrombus in LV

8. **Dynamic LV outflow tract obstruction (LVOT)** is uncommon and occurs due to hypokinesia of basal and mid segments of LV which decrease the cross sectional area of LVOT. The resulting increased velocity of blood flow through the outflow tract decreases pressure below the mitral valve and results in the leaflet being drawn anteriorly towards the septum (venturi effect) which further increases the LVOT obstruction and MR. 2D-echo helps evaluate the hyperkinetic segments, the LVOT obstruction and presence of systolic anterior motion (SAM) of the mitral leaflet. *Treatment* – Decreasing myocardial contractility and heart rate with beta blocker while expanding intravascular volume with several small doses of normal saline to increase preload and decrease LVOT obstruction and SAM.

B. Arrhythmic complications

Arrhythmias have an adverse hemodynamic consequence. Patients with LV dysfunction have a relatively fixed stroke volume and depend on changes in heart rate to alter CO. Tachyarrhythmias after AMI include VF, VT and AF or AFL. In general, these are treated according to advanced life support (ACLS) guidelines. It is reasonable to manage refractory arrhythmias by aggressive stimulation with beta-blockers, IABP use, emergency PCI-CABG surgery and maintaining serum potassium levels > 4.5 mEq/L. Routine use of prophylactic anti-arrhythmic drugs is not indicated for suppression of isolated (PVC) couplets, runs of accelerated VT and non-sustained VT.

Accelerated idioventricular rhythm (AIVR) occurs in about 20% of pts and is often observed shortly after reperfusion and is not routinely treated. Nonsustained VT (NSVT) occurring early does not appear to be associated with increased mortality risk.

VT late in course of AMI is more common in patients with transmural infarction and LV dysfunction and more likely to be sustained and cause marked hemodynamic deterioration. Rapid abolition with cardioversion/defibrillation is mandatory because it frequently deteriorates into VF. Patients with recurrent or refractory VT should be considered for specialised procedures such as implantation of AICD or surgery. Urgent attempts at revascularization (angioplasty or CABG) can help control refractory VT.

Ventricular fibrillation can occur in 3 settings in hospitalized pts with AMI. (a) Primary VT occurs suddenly and unexpectedly in patients with no features of LVF. (b) Secondary VF is often the final event of a progressive downhill course with LVF and cardiogenic shock. (c) Late VF develops after > 48 hrs and mostly occurs in patients with large infarcts and LV dysfunction. *Treatment* - Unsynchronised electrical counter shock with at least 200–300 joules as rapidly as possible. Amiodarone IV can be used for interruption of recurrent episodes. When synchronous cardioactivity is restarted by counter shock but contraction is ineffective (pulseless electrical activity), usual cause is extensive myocardial ischaemia or necrosis or rupture of the ventricular free wall or septum.

Prophylactic implantation of an ICD after AMI in patients with LEVF < 35% on echocardiography done at least 40 days post-AMI with New York Heart Association (NYHA) class II or III symptoms.

Supraventricular Tachyarrhythmias

(a) Sinus tachycardia occurs due to anxiety, persistent pain, LV failure, pericarditis, hypovolaemia and cardioacclerater drugs such as atropine, epinephrine or dopamine. It results in augmentation of myocardial O_2 consumption and reduction in duration of coronary perfusion. Persistent sinus tachycardia can signify persistent heart failure and suggests poor prognosis. *Treatment* - Analgesics for pain, diuresis for heart failure, beta-blockers and nitroglycerine for ischaemia and aspirin for fever and pericarditis.

(b) AF and AFL are usually transient and due to augmented sympathetic stimulation in the atria, LV failure, pericarditis and ischaemic injury to the atria and RVMI. There is significant reduction in CO. AF is associated with increased mortality and stroke, particularly in patients with AWMI.

Tr. Rate control with IV Diltiazem or esmolol. If patient is haemodynamically unstable, immediate intrathoracic cardioversion. If AF is present for > 48 hrs, or if the duration is unclear cardioversion should be preceded by TEE to rule out LA thrombus. If patient is haemodynamically stable, cardioversion can be done pharmacologically (amiodarone, ibutilide and procainamide) or with electrical cardioversion. Anticoagulation is necessary for 3 or more weeks, before and for another 4 weeks after cardioversion to prevent thromboembolic complications, if duration of AF is > 48 hrs, if less cardioversion without anticoagulation.

Bradyarrhythmias

(a) Sinus bradycardia if isolated and associated with hypotension, IV atropine.

(b) AV and intraventricular blocks - (i) 1° AV block generally does not require specific treatment. If associated with hypotension, atropine can be given. (ii) 2° AV block – (a) Type I - Atropine if patient becomes symptomatic, ventricular rate fall < 50 bpm, PVCs and BBB develops, heart failure. (b) Type II - Because of its tendency to complete heart block, temporary external or transvenous temporary pacemaker. (c) CHB - In patient with IWMI, it is usually transient with rate > 40 pm and a narrow QRS complex, pacing is not necessary unless patient has ventricular rate < 40 to 50 bmp. Permanent pacemaker is almost never indicated. (d) In patients with AWMI the CHB often occurs suddenly and is usually preceded by intraventricular block and often type II AV block. Such patients have unstable escape rhythms with wide QRS complexes and rate < 40 bpm and ventricular asystole. Temporary pacing protects against transient hypotension and asystole but has no survival benefit. (e) Intraventricular block - RBBB alone can progress to AV block because it is often a new lesion, associated with anteroseptal infarction and is associated with increased risk. Bifascicular block carries increased risk of developing CHB, severe pump failure and high mortality and temporary pacing is advisable. Permanent pacemaker insertion may be required, if CHB persists, when sinus node function is markedly impaired or when type II 2nd or 3rd degree block occurs intermittently.

C. Ischaemic Complications

Recurrent post infarction angina may be due to either an infarct extension or reinfarction in a separate area or reocclusion of infarct related artery. If the ECG reveals ST segment re-elevation or presence of new Q waves or there is re-elevation of cardiac markers, PCI is advisable. If unavailable repeated fibrinolysis can be considered. Haemodynamically stable symptomatic patients are treated with nitroglycerine and beta-blockers. When hypotension, heart failure or ventricular arrhythmias develop during recurrent ischaemia, urgent catheterization and revascularization are indicated. With increasing use if PCI, stent thrombosis may be a cause of ischaemia.

D. Inflammatory

Pericarditis after MI is classified as early or late. Early pericarditis usually develops 24 to 96 hrs after MI. Pain

is postural, worse when supine and relieved when sitting up and leaning forward. Radiation of pain to the trapezius ridge is almost pathognomic. ECG shows ST elevation with concave upward curve. The changes are generalized. *Tr.* – Aspirin 650 mg q4–6 hrs. Colchicine may be used in those with recurrent pericarditis. Late pericarditis (Dressler's syndrome) occurs 1 to 8 weeks after AMI. Patients present with precordial chest discomfort, malaise, fever, leucocytosis and raised ESR. 2D-echo may reveal pericardial effusion. Treatment – Aspirin. If > 4 weeks have elapsed since AMI, NSAIDs and even steroids may be used for severe symptoms.

E. Embolic Complications

Systemic embolism most often results in stroke, although there may be limb ischaemia, renal infarction or mesenteric ischaemia. *Treatment* – Heparin IV for 3 to 4 days followed by oral anticoagulation for 3 to 6 months in patients with mural thrombus and those with large akinetic areas detected by 2D-echo.

Management of STEMI

Following hospital admission

1. ***Admission to coronary care unit*** – Mortality from acute cardiac infarction can be reduced by monitoring of cardiac rhythm and early treatment of disorders of the heart beat.
2. ***Relief of pain*** – Pethidine 100 mg. IM or morphine 15 mg subcutaneously, may be repeated if pain not relieved within 30 minutes. Risk of vomiting can be reduced by combining with 10 mg trifluprom azine. Rarely slow intravenous injection of 1–2 mg morphine may be necessary if pain is very intense. Nitrates and thrombolysis may also relieve pain.
3. ***IV drip*** – Slow IV infusion using 5% dextrose is started.
4. ***Oxygen*** – If cyanosis, severe or persistent pain, or pulmonary venous congestion. O_2 supplementation is considered if saturation <92%.
5. ***Blood samples*** – Should be taken on admission to hospital for baseline determination of electrolytes, renal function and cardiac enzymes.
6. ***Rest*** – Duration must be adjusted to the individual case depending on size of infarct and complications. Early mobilization helps prevent complications associated with long periods of bed rest and helps psychological recovery.
7. ***Sedatives*** – For relief of anxiety. Diazepam 5 mg t.d.s.
8. ***Limitation of infarct size*** – Reperfusion therapy in all patients presenting within 12 hrs of onset of symptoms. Indications for primary PCI:
   - Patients presenting within 12 hrs of symptoms onset and anticipated time from first medical contact to balloon inflation of 2 hrs or less.
   - Contraindications to fibrinolytic therapy.
   - Patients presenting within 12–24 hrs of symptom onset with ongoing symptoms/signs of ischaemic or hemodynamic instability.
9. ***Antiplatelet drugs*** – Aspirin dose (75–100 mg) and Clopidogrel 75 mg or Prasugrel 60 mg stat followed by 5-10 mg/day, or Ticagrelor 90 mg bd.
10. ***Antithrombotic therapy*** – Choice of fibrinolytic agent: Tenecteplase has the advantage of being fibrin specific, can be given as a bolus dose, has a low incidence of hypersensitivity reactions. Dose 0.53 mg/kg body weight.

    Other alternatives are: (1) Reteplase (r-PA) - 10 U bolus dose at arrival and 10U bolus after 30 minutes, (2) Alteplase (t-PA) - Bolus of 15 mg, infusion of 0.75 mg/kg for 30 minutes (maximum, 50 mg), then 0.5 mg/kg (maximum, 35 mg) over the next 60 minutes; the total dose not to exceed 100 mg. (3) Streptokinase - 1.5 million units IV given over 30–60 min.

Contraindications to thrombolysis

(a) *Absolute contraindications*

- Haemorrhagic stroke or stroke of unknown origin at any time.
- Ischaemic stroke in preceding 6 months.
- CNS trauma or neoplasm.
- Recent trauma, surgery/head injury within preceding 3 months.
- GI bleeding within the last month in known bleeding disorder.
- Aortic dissection.
- Non-compressible punctures (e.g. liver biopsy, lumbar puncture).

Relative contraindications

- TIA in preceding 6 months
- Oral anticoagulant therapy
- Pregnancy or within 1 week post-partum
- Uncontrolled hypertension (BP > 180/110 mm Hg)
- Advanced liver disease
- Infective endocarditis

- Peptic ulcer
- Refractory resuscitation

(b) Elderly patients: There is increase in mortality rate as age increases. As per American Heart Association–
   i. Thrombolytic therapy as compared to no reperfusion therapy offers mortality benefit in elderly subjects upto age of 85.
   ii. Nonfatal strokes are rare.
   iii. Reduced doses of unfractionated heparin or adjusted doses of LMWH minimize risk of bleeding

(c) Time sensitivity - Thrombolytic therapy is more time sensitive as compared to PCI.

(d) Hemorrhage is another important issue with thrombolysis.

(e) Reinfarction and recurrent ischaemia - Following thrombolytic therapy, there is a pro-thrombotic period. Reocclusion of the infarct related artery may be 10–30% by 3 months.

Beta-adrenergic antagonists

1. Oral β-blockers should be administered in first 24 hrs to patients who do not have heart failure, a low output state, are not at increased risk of developing cardiogenic shock or have no other contraindications to beta-blocker therapy. Care should be taken to avoid hypotension. ACE inhibitors improve survival in patients who have LVEF ≤ 40% and those who are in heart failure. ARBs may be used in patients who do not tolerate ACE inhibitors.
2. IV or oral nitrates do not improve outcomes. Nitrates may be used for pain.
3. High dose statins should be started as early as possible as part of secondary prevention measures.

Management post-fibrinolytic therapy

1. Routine angiography and PCI of the infarct related artery may reduce the rates of reocclusion or reinfarction.
2. Pharmacoinvasive therapy has an important place in improving prognosis of patients after thrombolysis. It is increasingly demonstrated that patients after a successful thrombolysis should be transferred to facilities with a cardiac cath lab for coronary angiography and if need be a PCI with stent deployment.

However because of resource intensiveness of this strategy and absence of an effect on survival, most guidelines still favour a more conservative approach consisting of revascularization guided by the results of risk stratification by early exercise testing. Angiography (and revascularization) should of course be performed in the event of spontaneous ischaemia or development in mechanical complications.

Percutaneous transluminal coronary angioplasty

(1) *As interventional post-thrombolytic procedure* – if intermittent or continuous chest pain or discomfort and persistent ST elevation on ECG.

(2) *Primary coronary angioplasty* – Indications – (i) Patients with previous bypass surgery, or large infarcts (anterolateral or extreme inferoposterior) especially with hemodynamic compromise; this must be done within 60-120 min of presentation. (ii) Patients with ST elevation acute MI and absolute contraindication to lytic therapy (bleeding hazard). (iii) Emergency angiography and angioplasty (when appropriate) in patients with long presentation delay (>12 hrs) or in cases of atypical presentation and diagnostic uncertainty (Figs. 109 and 110).

(3) *CABG surgery* – Indications: (i) Coronary occlusion developing during cardiac catheterization, coronary angiography or during PTCA. (ii) Patient continues to have ischaemic pain and is haemodynamically unstable and rescue angioplasty has failed, or is not feasible, or if angiography shows left main disease or multivessel disease. (iii) Infarction occurring in a 'stuttering' manner over a few days producing increasing hemodynamic instability.

Therapeutic lifestyle changes – Smoking cessation, exercise dietary modification and drugs for secondary prevention. Patient counselling and education are key to maintaining adherence to therapy in the long run.

Recent advances in management of myocardial infarction

Cardiac repair and regeneration

1. **Stem cell therapy:** Variable degrees of improvement in cardiac function in models has been observed with transplantation of stem cells from different tissues. Intracoronary infusion of bone marrow derived mononuclear cells (BMC) within 7 days after reinfusion therapy for AMI is associated with significant improvement in LV remodelling parameters within first 4 months after AMI.
2. **Sono-thrombolysis.** Use of ultrasound waves (through transcutaneous route) along with fibrinolytic agent, the ST segment resolution was better than those who received Tenecteplase alone. Possible mechanism is release of nitric oxide by various endothelial cells and opening of collateral channels.
3. **Optimising the outcomes of PPCI**
   (a) *Thrombus aspiration during PPCI:* Thrombus aspiration catheters have been used to improve outcome of PCI. They have reduced distal embolization and resulted in enhanced TIMI grade 3 flow, and more complete ST resolution. Results of

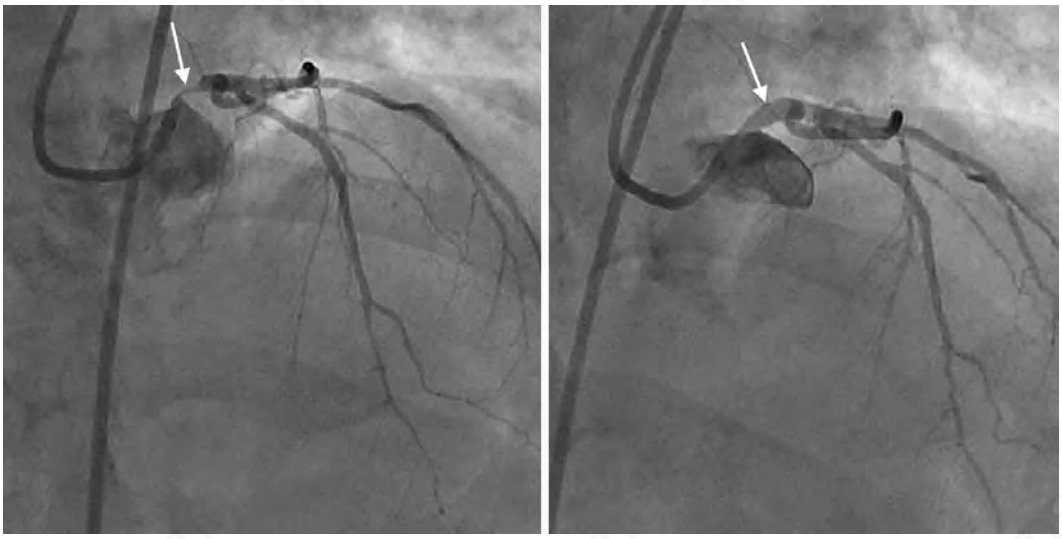


Fig. 109: Coronary angiography showing left main coronary artery stenting

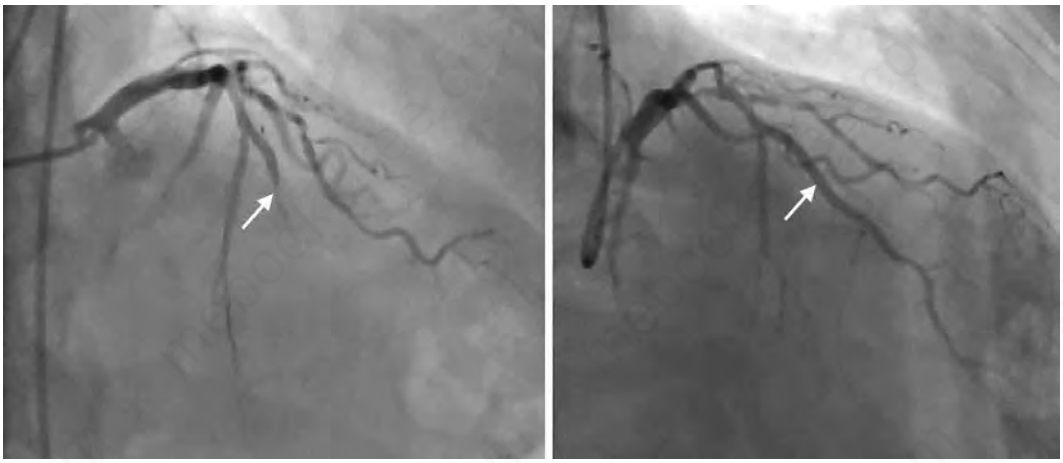


Fig. 110: Primary angioplasty after myocardial infarction (PAMI)

thrombus aspiration compared to Balloon Angioplasty – Adjunctive aspiration resulted in enhanced rates of angiographic myocardial perfusion (blush) and ST segment resolution.

(b) *Intracoronary GIIb/IIIa inhibitors*: Intracoronary administration of drugs increases local drug concentrations several fold. The increased concentration of inhibitors like Abciximab, Eptifibatide, Tirofiban are shown to improve outcomes of PCI safely and efficaciously in terms of reduction in infarct size and improved TIMI flow.

(c) *Adenosine*: Intracoronary administration of vasodilators such as adenosine during and after PPCI has been shown to improve flow in the infarct-related coronary artery and myocardial perfusion.

(d) *New oral anti-platelet drugs:* Prasugrel and Ticagrelor while the thienopyridines is not a prodrug and therefore has a faster onset of action with less variability. It causes stronger platelet inhibition, particularly in the early phase and its reversible which may be an advantage in reducing bleeding.

4. **Cardioprotection against myocardial reperfusion injury:** Restoration of blood flow to ischaemic myocardium sometimes leads to myocardial injury (ischaemic-reperfusion injury). It can take the form of (a) myocardial stunning (transient LV dysfunction after restoration of blood supply). (b) No reflow phenomenon (inability to restore blood supply at microvascular level even after opening of myocardial infarct related artery). (c) Reperfusion arrhythmia. (d) Lethal reperfusion injury leading to extension of infarct.

Remote ischaemic preconditioning is carried out (a) With brief occlusion of blood flow either to upper or lower limb by periodically inflating and releasing the BP cuff. (b) Transient balloon occlusion of the infarct related artery. (c) Use of pharmacological agents. Cyclosporine inhibits opening of mitochondrial PTP and protects myocardium from reperfusion injury. Use of cyclosporine is associated with reduction in infarct size.

10. CARDIAC ARREST

Cardiac arrest is defined as sudden failure of the heart resulting in inadequate cerebral circulation. Cardiac standstill is responsible for majority of cases, the other mechanisms being ventricular fibrillation and electromechanical dissociation.

CAUSES

See Table 74 for the causes of sudden cardiac death and Table 75 for specific causes in young.

CLINICAL FEATURES

Early

- Loss of consciousness.

Table 74: Causes of sudden cardiac death

• Myocardial infarction.
• Airway obstruction and inadequate ventilation, e.g. foreign body.
• Major obstruction to blood flow through central circulation - (a) Acute massive pulmonary embolism. (b) Following acute event e.g. arrhythmia in presence of chronic obstruction to circulation such as PS, MS or AS.
• Surgery – (a) Anaesthesia – Too rapid or unregulated administration or overdose. (b) Manipulation of viscera in chest or abdomen. (c) Massive arterial haemorrhage. (d) Hypotension. (e) Endotracheal intubation. (f) Air or fat embolism.
• Diagnostic procedures – Bronchoscopy, bronchography, IV pyelography, cardiac catheterization, angiocardiography.
• Haemorrhage – sudden and severe.
• Electrolyte imbalance – Hypokalaemia or hyperkalaemia.
• Electric shock, anaphylaxis.
• Drowning.
• Hypothermia.
• Drugs – Due to overdosage or sensitivity – digitalis, quinidine, procainamide, adrenaline, potassium, local anaesthetics, saccharated iron oxide and rarely antibiotics.

- Absence of pulsation in carotid, temporal or femoral artery.

Late

- Dilated pupils.
- Unrecordable BP
- Convulsions.

MANAGEMENT

1. Immediate Management
   - *Positioning* – Put patient in supine position on firm surface such as wooden board or on the floor.
   - *Chest thump* – Strike the left upper chest forcibly with the fist. This may restart the heart if arrest is due to asystole.
   - *Basic CPR:*
     - Compression
     - Airway
     - Breathing

Compression – first goal of CPR is to maintain perfusion of vital organs. Chest compression allows the heart to maintain an externally driven pump function by sequential emptying and filling of its chambers.

Place the heel of the hands one over the other on the lower end of sternum and compress the sternum about 4–5 cm at a rate of 100/min.

For single rescuer, from infancy (excluding newborns) through adulthood and for adults responded to by two rescuers, a compression-ventilation ratio of 30:2 is now recommended.

For two-rescuer CPR in infants and children, the former compression-ventilation ratio of 15:2 is recommended.

Airway Maintenance

Patient breathing– Airway patency can often be obtained by simple methods – Put patient in supine position on

Table 75: Causes of sudden cardiac death in the young

1. Congenital heart disease
2. Congenital anomalies of coronary arteries.
3. Marfan's syndrome
4. Myocarditis
5. Cardiomyopathy – hypertrophic or dilated
6. Arrhythmogenic RV dysplasia

a firm surface such as a wooden board or on the floor. (i) Jaw lift. Placing the fingers bilaterally behind mandibular angles, displace the mandible forward and anteriorly. Clear the pharynx with a finger covered with gauze piece. (ii) Give Oxygen. (iii) Do endotracheal intubation unless contraindicated (injury to cervical spine, mechanical upper airway obstruction, severe restriction of cervical mobility or inability to open the mouth). In such a case nasotracheal intubation.

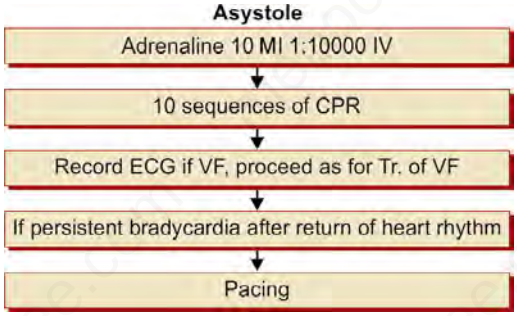
Patient Not Breathing

Mouth-to-mouth respiration – Use fingers of left hand to hold the chin forwards while extending the neck slightly with the rt. hand. By placing the edge of your hand the forehead it is possible to maintain the extended position, at the same time pinching the nose tight. Now place your lips firmly over the mouth (a handkerchief or gauze pad can be put over patient's mouth) and having taken a large breath, exhale. Look for the chest rising as you exhale. Now release your seal and wait for passive exhalation, again checking if the chest is moving. Repeat the procedure once exhalation is complete; this usually means 12 to 15 breaths per minute. Not considered very important.

Oronasal resuscitation – The nose can be used as airway particularly when one cannot get the airtight seal over the mouth or if the mouth contains blood or vomit. Use the left hand to hold the chin forwards and upwards and keep the mouth shut. If this is not possible, use a pad over the mouth to seal it. Place your mouth over the entire nose and exhale. Then follow the same procedure as in mouth-to-mouth resuscitation.

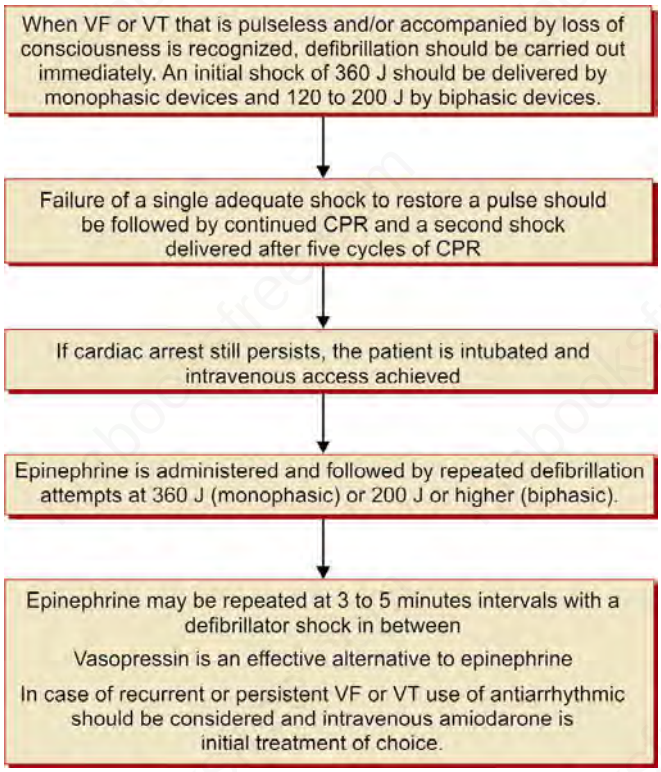
If a suitable face mask is available keep the same over the patient's mouth and nose snugly, push the lower jaw forwards and upwards with the thumb and index finger and blow the Ambu bag which is connected with the face mask. Oxygen should be connected with the Ambu bag.

2. Determination of Heart Action by ECG:

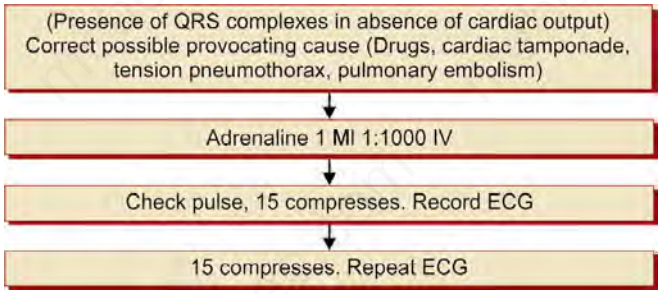


Note: Recovery from asystole is rare. It is futile to continue resuscitation for more than 15 mins.

Ventricular fibrillation



Electromechanical Dissociation



Vasopressin 40U IV is alternative to epinephrine for pulseless electrical activity. There is no role of atropine in case of asystole and given in case of bradyarrhythmia only. Sodium bicarbonate used only in cases of severe systemic acidosis, hyperkalemia with pH, pO_2 and pCO_2 monitoring at 1 mEq/kg IV.

Duration of Resuscitation

In absence of indication to stop earlier, attempts should be continued for about 30 minutes provided there is good evidence of adequate tissue oxygenation (satisfactory pH and blood gases). Exceptions are arrests associated with drowning, hypothermia and certain drug overdosage. Without adequate oxygenation, irreversible brain damage

sets in after about 3 minutes and resuscitation attempts longer than 10 minutes are likely, if successful, to result in a severely disabled individual.

11. HEART FAILURE

A clinical syndrome in which due to abnormality of cardiac function, a low cardiac output and congestive symptoms are prominent.

PATHOPHYSIOLOGY

Compensatory body responses to heart failure:

1. *Alteration in heart structure* (hypertrophy, size, shape, fibrosis).
2. *Starling's mechanism* – Major determinants of cardiac output are stroke volume and heart rate. Stroke volume is determined by preload (ventricular volume at end of diastole), contractility and afterload (factors resisting ventricular ejection). When reduced myocardial contractility reduces stroke volume, cardiac output is partly maintained by the Starling mechanism. However, the resulting elevation of LV filling pressure may cause dyspnoea and other congestive symptoms.
3. *Activation of neuro-endocrine system* – in particular the sympathetic and renin-angiotensin systems. Plasma vasopressin and aldosterone are increased. These responses maintain blood pressure by causing vasoconstriction, but they can be harmful because of the extra work imposed on the heart, and renal vasoconstriction leading to fluid retention.
4. *Increased peripheral resistance and redistribution of blood flow* – Systemic vascular resistance is increased, and there is redistribution of blood flow away from skin, muscle and splanchnic circulation. Reduced blood flow to kidneys causes sodium retention.
5. *Desensitization of vessels and myocardium to agonists* – e.g. catecholamines (stimulation of sympathetic system).

LEFT HEART FAILURE (ACUTE HEART FAILURE)

Causes

See Table 76 for the causes of acute heart failure.

Table 76: Causes of acute heart failure

Myocardial damage
Myocardial infarction
Myocarditis
Cardiomyopathy
Cardiac depressant drugs
Increased load
Hypertension
Mitral and aortic valve disease
Cardiac arrhythmias
Over transfusion

Clinical Features

- Severe dyspnoea (with at times pink frothy sputum)
- Tachypnoea
- Cold clammy skin
- Tachycardia
- Low blood pressure
- Lung crackles
- Raised jugular venous pressure
- Gallop rhythm

Emergency Treatment

- Monitor ECG
- Oxygen 5–6 litres/min by mask
- Frusemide 40–80 mg iv
- Morphine 1–2 mg iv or pentazocine 30 mg IM
- Monitor urine output
- Insert intravenous line
- Consider: Dopamine 5–20 µg/kg/min iv or other inotrope (e.g. milrinone), or intra-aortic balloon pump

Investigations

History

- Chest pain, suggesting MI
- Palpitations, suggesting arrhythmias (e.g. ventricular tachyarrhythmia, atrial fibrillation)
- Drug history (e.g. cardiotoxic agents, NSAIDs)
- Previous cardiac history (e.g. valve operation, myocardial infarction)
- Chest trauma (possible cardiac tamponade)
- Serum biochemistry, blood count and cardiac biomarkers
- Echocardiogram in selected cases (e.g. valve dysfunction, suspected tamponade)

Beta natriuretic peptide (BNP) - In patients with heart failure and renal dysfunction, BNP levels give the true clinical picture, because BNP levels correlate with decreased ejection fraction in systolic dysfunction. However if BNP is

raised but ejection fraction is normal, then the rise in BNP can be due to systolic dysfunction or pulmonary embolism. In case of a raised BNP in a breathless patient diuretic therapy is initiated and patient admitted to ICU.

Interpretation of BNP levels

Normal	<100 ng/mL
Suspected heart failure	100-400 ng/mL
Probable heart failure	>400 ng/mL

When BNP >1000 ng/mL it indicates likelihood of repeated attacks of LVF.

Patients with raised BNP and hypotension are treated with inotropes.

Patients with low CVP and raised BNP are monitored by checking pulmonary pressure

Further management – depends on the underlying cause, e.g. if ischaemic, coronary angioplasty or bypass surgery may be indicated. Supportive therapy with diuretics, vasodilators (especially ACE inhibitors) and for short period IV inotropic agents.

RIGHT HEART FAILURE (CHRONIC HEART FAILURE)

Causes

See Table 77 for the causes of chronic heart failure.

Symptoms

1. Due to inadequate blood supply to the tissue – Weakness, fatigue, and decreased urinary output resulting in fluid retention and oedema.
2. Due to inability of the heart to empty properly – resulting in increased venous pressure and congestion of tissues.
   (a) *Cerebral* – Headache, insomnia, restlessness, sluggish mental state.
   (b) *Pulmonary* – Cough, dyspnoea (Table 78), rarely orthopnoea, Cheyne Stokes respiration.
   (c) *Portal* – Anorexia, nausea and vomiting, fullness after meals. Pain in right hypochondrium commonly aggravated on exertion (herpetic angina). In patients with long-standing congestion caused by for example cardiomyopathy, there may be steatorrhoea and protein loss.
   (d) *Renal* – Nocturia and oliguria.
   (e) *Peripheral* – Oedema of feet or generalised anasarca.

Table 77: Causes of chronic heart failure

- Pulmonary hypertension
  - Secondary to left heart failure
  - Chronic lung disease (cor pulmonale)
  - Pulmonary embolism
  - Left-to-right shunts
- Primary pulmonary hypertension
- Right ventricular infarction
- Pulmonary or tricuspid valve disease
- Isolated right ventricular cardiomyopathy

Signs

1. *Raised JVP* – Positive hepatojugular reflux.
2. *Enlarged and tender liver* – Systolic pulsation of liver if tricuspid regurgitation.
3. *Oedema* – The erect position favours collection of fluid in feet, ankles and lower portion of legs, whereas recumbent position favours accumulation in sacral region. If oedema is severe, it may be associated with hydrothorax (more often on right side), and hydropericardium and occasionally ascites.
4. *Evidence of heart disease* – Signs associated with underlying disease. Cardiomegaly with evidence of right ventricular or combined ventricular enlargement. Right ventricular gallop. Murmur of relative TR common.
5. *Peripheral cyanosis* – May occur due to slow peripheral circulation.
6. *Cardiac cachexia* – Loss of subcutaneous fat and muscle tissue.

Investigations

Confirm diagnosis

- Chest radiograph
- Echocardiogram

Table 78: The New York Heart Association classification of dyspnoea

Class	*Patient symptoms*
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Look for underlying cause

- ECG – Ischaemia/infarction, LV hypertrophy, arrhythmia
- Echo – Valvular disease, dilated cardiomyopathy, ischaemic heart disease
- Blood tests – for rare causes, e.g. hypocalcaemic cardiomyopathy, thyroid heart disease, anaemia, iron storage diseases, amyloid, sarcoid
- Coronary angiography (occasionally) and ventricular biopsy (rarely)

Assessing severity

- Rest or exercise radionuclide ventriculography or echocardiography for ejection fraction
- Cardiopulmonary exercise testing for maximal oxygen consumption

Prognosis

- 24-hour Holter monitoring for ventricular arrhythmias
- Blood tests for associated disease: Kidney, liver, electrolyte disturbances
- Neurohormonal markers: Natriuretic peptide levels. A BNP concentration of > 22 pg/mL is diagnostic of heart failure and it rises in proportion to the severity of the disease.

Assessing ventricular dysfunction

Systolic dysfunction of LV – LV ejection fraction is the most convenient and reliable. Other methods include peak rate of pressure rise within the ventricle (positive dp/dt max), filling pressure (e.g. LV end-diastolic pressure, pulmonary capillary wedge pressure), ventricular volumes by echocardiography, radionuclear ventriculography or other imaging modalities.

Diastolic dysfunction of the heart – Commonly quantifying methods used are hemodynamic echocardiography, radionuclear or ventriculographic methods. Most commonly used methods are the rate constant of isovolumic relaxation of the ventricle during early diastole, the early-to-late peak filling velocity across the mitral valve on Doppler echocardiography, and the peak rate of ventricular filling on radionuclear-gated acquisition scans.

Management: of congestive heart failure.

GENERAL MEASURES

- Rest – Physical and mental. Rest in bed and in chair till there is no longer venous engorgement, oedema or congestion of lungs and heart rate constantly under 80 per minute for some days.
- Diet – Restricted salt intake (2 gm salt per day). Salt substitute may be used for palatability. Fluid intake upto 1500–2000 mL. daily may be allowed. Frequent, small, bland, low caloric feeds preferred at onset of therapy.
- Other measures – No excessive alcohol intake. No smoking. Maintenance of optimal body weight. Control of BP.

Drug Therapy

Digitalis and diuretics

See Table 79 for digitalis and diuretics.

Vasodilators

The change in cardiac output in heart failure results from reduction of ventricular filling pressure (preload) and blood pressure (afterload). The haemodynamic effect of any individual vasodilator depends on the relative effect to relax veins or arterioles. Hydralazine (up to 200 mg t.d.s.) affects arterioles and prazosin (0.5 mg gradually increased to 10 mg t.d.s.) mainly the veins. Nitrates and ACEIs are intermediate.

(a) *ACEIs* – reduce venous pressure, increase cardiac output, lower BP, increase renal perfusion, and increase blood flow to exercising skeletal muscles. Like other vasodilators, tolerance does not develop. *Side effects*– Renal failure may be aggravated and plasma potassium may increase (hence potassium supplements should be stopped). In some patients, the first dose may lower cardiac output dramatically, causing fainting. In severely diuresed patients, the drug should be started in low doses, omitting the morning dose of diuretic which is started again the next day. Dose of ACEI can be increased gradually over the following days. ARBs can be used if intolerance to ACEIs.

Indications – ACEIs are the most effective vasodilator therapy in heart failure and should be used relatively early. However, they should be used cautiously in presence of kidney failure or hyperkalaemia.

(b) *Calcium antagonists* – are potent vasodilators and may be useful in patients with heart failure complicating hypertension or ischaemic heart disease. However, they have intrinsic negative inotropic effect and must be used with caution in patients with hypotension, low ejection fractions, or pulmonary congestion. Amlodipine is the safest.

(c) *Carvedilol and β-blockers* – For patients with symptomatic heart failure who are not decompensated (Class II to III). Dose – Initial 3.125 mg bd, slowly titrated every 2 weeks to target dose of 25 mg bd. Metoprolol succinate 12.5 to 100 mg or Bisoprolol 12.5 to 10 mg/day.

Table 79: Digitalis and diuretics in CHF

Drug	*Generic name*	*Avg. daily dose (mg)*	*Action duration (hr)*	*Side effects*
Digitalis				
Digoxin		**Loading** PO: 0.25–1.5 mg/d divided doses IV: 1.2 mg, then 0.5 mg q6h till digitalization **Maintenance** 0.25–0.5 mg/d for 5–6 days in the week		**Extra-cardiac** Anorexia, nausea, vomiting, occasional diarrhoea. Altered colour vision (yellow or green) **Cardiac** Bradycardia or SA block, Multiple PVCs, Ventricular bigeminy, PAT, PVT, Vent. Fibrillation
Diuretics Type of diuretic and mode of action				
Thiazides type (medium efficacy)				
Inhibition of NaCl cotransport in distal convoluted tubule	Chlorothiazide Hydrochlorothiazide Benzthiazide Hydroflumethiazide Bendroflumethiazide Trichlormethiazide Methyclothiazide Polythiazide Cyclothiazide	500-15005 0-150 50-200 25-50 2.5-15 2-4 5-10 2-8 2-6	6-12 12-24 6-12 6-12	Hypokalaemia Hyponatremia volume depletion Contraction alkalosis Hypomagnesaemia Glucose intolerance Hypercalcaemia Hyperuricaemia Rarely impotence, acute interstitial nephritis
Related sulphonamide compounds				
	Chlorthalidone Indapamide Quinethazone *Metolazone	50-100 2.5 50-150 2.5-20	 18-24 24-48	Hypokalaemia Hyperlipidaemia
Loop diuretics (High efficacy)				
Inhibition of Na-K-2Cl cotransport in ascending limb or loop of Henle	Furosemide Bumetanide Ethacrynic acid Torsemide	20-160 0.5-3 25-150 5-200	 6-8	Same as above but glucose intolerance less common Calciuretic
Potassium sparing diuretics (Low efficacy)				
	Spironolactone Eplerenone	50-200 50-100	24 24	Gynecomastia Mastodynia Diminished libido Irregular menses
Blocking of sodium channels in cortical collecting tubule				
	Triamterene Amiloride	50-150 5-20	6-8 12-24	Triamterene stone Megaloblastosis GI irritation including diarrhoea Mild metabolic acidosis Dangerous hyperkalaemia (if combined with K supplements, drugs that decrease K excretion (e.g. β-blockers, ACEIs, non-steroidal, or if impaired renal function).

*Does not increase GFR and is effective with GFR < 20 mL/min.

(d) Dobutamine 15–20 μg/kg/min. in patients with acute heart failure complicating congestive heart failure.

(e) Amrinone/Milrinone – for short term IV use.

Indications

- End-stage heart failure secondary to ischaemic heart disease
- Other cardiomyopathies such as idiopathic dilated, post-viral, post-partum
- Valvular and congenital heart diseases not amenable to established corrective surgical procedure

Contraindications

- Age >65 years

- High pulmonary vascular resistance
- Incurable malignancy
- Renal failure above and below the expected pre-renal failure
- Hepatic failure which exceeds that explained by cardiac failure or when accompanied by significant coagulopathy
- Other irreversible disease such as emphysema, intractable systemic illness or amyloidosis
- Patients who are emotionally unstable and have psychological abnormalities and cannot cope up with the demands and burdens of strict compliance with medications and follow up requirements
- Infection with HIV
- History of substance abuse
- Type II DM with tuberculosis
- Peptic ulcer disease
- Unresolved pulmonary infection
- Presence of active systemic infection
- Patients with positive PPD or clinical evidence of previous TB are to be treated prophylactically with appropriate drugs for 12 months

Other Measures

1. **Sedative –** For adequate sleep.
2. **Aminophylline –** 0.25 to 0.5 gm. in 10 mL distilled water IV may help in reducing bronchospasm, stimulating ventricular contraction and the respiratory centre and acting as mild diuretic.
3. **Antibiotics –** Adequate control of pulmonary infection at the earliest.
4. **Oxygen –** Indications – (i) Failure complicated by pulmonary lesions like infarction, oedema or pneumonia. (ii) With acute myocardial infarction. (iii) Secondary to lung disease like emphysema. (iv) Patients with persistent congestion of lungs.
5. **Physical therapy –** Massage of arms and legs to maintain peripheral circulation and prevent phlebothrombosis. Gentle passive or active exercises during convalescence.
6. **Control of reversible factors –** Treatment of anaemia, thyrotoxicosis, SIE, lung infection, hypertension, or surgical correction of congenital or acquired lesion.
7. **Cardiac transplantation –** Aetiology in most is either ischaemic or dilated cardiomyopathy. Contraindications – Irreversible changes in kidney and hepatic function, advanced age, active infection, recent pulmonary infarction (< 6 weeks), diabetes mellitus (relative contraindication), elevated pulmonary vascular resistance, peripheral vascular and cerebrovascular disease, co-existing disease that may limit life expectancy, emphysema and chronic bronchitis.
8. **Surgical alternatives to transplantation**
   (a) *Cardiomyoplasty* – is a technique in which skeletal muscle (commonly latissimus dorsi) is used to supplement the contractile power of diseased myocardium. Advantages include absence of need for donors, external power devices and immunosuppression. It may be offered when transplantation is contraindicated or unavailable.
   (b) *Mechanical devices* – (i) Existing ventricles may be excised and a mechanical substitute implanted [total artificial heart (TAH)]. (ii) A pump may be implanted to assist the function of either or both ventricles without excising the native ventricles (ventricular assist device, VAT).
   (c) *High risk myocardial revascularization* – Hibernating myocardium is severely ischaemic, poorly contractile yet viable myocardium that recovers contractile function with restoration of adequate perfusion.
9. **Other techniques**

   Transmyocardial laser revascularization (TMR) – Creates a series of minute channels between the left ventricular cavity and the myocardium.

   Aneurysmectomy – LV function can be improved by resection of a ventricular aneurysm. Best results are obtained if adequate revascularization can be performed concurrently, and in patients with good septal contraction.

   Baptista operation – Partial left ventriculectomy in patients with dilated cardiomyopathy. The reduction in LV volume is supposed to normalize the ratio of left ventricular muscle mass to cavity diameter, to a physiologically efficient level.

   Biventricular pacing – This form of transvenous pacing called cardiac synchronization therapy, reverses the deleterious effects of ventricular dyssynchrony in the failing heart.

REFRACTORY HEART FAILURE

Causes

- Underlying condition amenable to medical or surgical treatment, e.g. hypertension, MS or AS, masked thyrotoxicosis, IE, constrictive pericarditis, vitamin B deficiency.

- Precipitating causes such as severe anaemia, pulmonary infection, cardiac arrhythmia or recurrent pulmonary emboli.
- Complications of therapy such as digitalis toxicity or electrolyte imbalance.

Heart failure with preserved ejection fraction (Table 80): Patients with HFpEF have normal LV end-diastolic volume and normal (or near-normal) EF and stroke volume and commonly exhibit concentric remodeling of either LV chamber and/or cardiomyocytes.

Compared with those with a reduced EF, patients with preserved EF are older.

More likely to be female; however, HFpEF occurs in both men and women throughout the 5th to the 9th decades of life.

The most common antecedent disease leading to HFpEF is systolic hypertension, which is present in more than 85% of patients, whereas ischemic heart disease is much less common than in HFrEF.

Standard heart failure therapy shown to be effective in HFrEF has not been found to reduce morbidity or mortality associated with HFpEF.

Management – It mainly involves control of hypertension.

'Tachycardia failure' – can be mistaken for dilated cardiomyopathy or can exacerbate failure in pre-existing cardiomyopathy. Sustained tachycardia can lead to reversible left and right ventricular dilatation and failure especially in the elderly.

Table 80: Differential diagnosis in a patient with HF and normal LV ejection fraction

• Incorrect diagnosis of HF
• Primary valvular disease
• Restrictive (infiltrative) cardiomyopathies (amyloidosis, sarcoidosis, hemochromatosis)
• Pericardial constriction
• Episodic or reversible LV systolic function
• Severe hypertension, myocardial ischaemia
• High output states (Anaemia, thyrotoxicosis, A-V fistulae)
• Chronic pulmonary disease with right HF
• Pulmonary hypertension associated with pulmonary vascular disorders
• Atrial myxoma
• Diastolic dysfunction of uncertain origin
• Obesity

Hypertensive hypertrophy with cavity obliteration (HHCO) – This is a new clinical entity with gross concentric uniform left ventricular hypertrophy with distal cavity obliteration. These patients have diastolic dysfunction with supernormal systolic function (LVEF 80%).

CHF without raised JVP

Acute MI and diabetic ketoacidosis combination.

12. SHOCK

A life-threatening state in which there is a serious reduction of cardiac output with inadequate perfusion of organs such as kidneys, brain and liver. It can occur either because the function of the heart itself is impaired, or because the heart is inadequately filled.

CLINICAL FEATURES OF SHOCK

See Table 82 for the clinical features of shock.

TYPES OF SHOCK AND THEIR MANAGEMENT

1. **Hypovolaemic** – due to decreased circulatory blood volume, e.g. internal GI bleeding or external hemorrhage, severe burns, dehydration from vomiting or diarrhoea or diabetic ketoacidosis; acute pancreatitis.

Table 81: Causes of biventricular failure

1. Myocarditis
2. Ischaemic heart disease
3. Cardiomyopathy
4. COPD
5. Severe arterial hypertension
6. Hyperdynamic circulation e.g. severe anaemia, hyperthyroidism.

Table 82: Clinical features of shock

• Cold clammy skin, profuse sweating
• Hypotension (systolic BP <100 mmHg)
• Tachycardia with thready pulse
• Rapid, shallow respiration
• Restlessness, drowsiness, confusion
• Oliguria, may progress to anuria
• Jugular venous pressure elevated in cardiogenic shock, reduced in hypovolaemic and anaphylactic shock, variable in septic shock
• Multiorgan failure

MANAGEMENT

1. *Rapid fluid replacement* – 2 litres of normal saline or Ringer lactate.
2. *Treatment of cause* – e.g. tetracycline for cholera, treatment of GI blood loss, insulin in diabetic ketoacidosis.
3. *Infusion* – Of colloids (Haemaccel or 5% albumin) if hypovolaemia associated with hypotension.

   Crystalloids can be given via one vein and colloid solution another. After initial infusion of 2 L of normal saline in severe hypovolaemic shock, alternate N saline with Ringer lactate or 5% dextrose saline. Hypokalaemia is common hence 40–60 mEq of potassium in dextrose saline infusion. Repeated if necessary depending on serum potassium levels.
4. *Blood transfusion* to bring up Hb once volume replacement is achieved. If type specific blood is not available in an emergency Type O Rh-negative blood can be given.

2. **Cardiogenic shock**

   Causes — e.g. acute myocardial infarction, acute myocarditis, acute MR, cardiac tamponade (For management see under acute MI).
3. **Septic shock** is a state of profound tissue hypoperfusion that results from septicaemia or presence of micro-organisms in blood stream.

PREDISPOSING FACTORS

- *Pre-existing disease* (impairment of immune mechanism): Diabetes, alcoholism, malnutrition, uraemia, liver disease.
- *Drug therapy* – Steroids, chemotherapeutic agents (impairment of immune function). Antibiotics (altered gut flora leading to colonization by pathogenic organisms).
- *Invasive procedures* (breach or disrupt host defence mechanisms) – Instrumentation of urinary tract, arterial and venous lines, nasotracheal tubes. Enteral feeding (upper intestinal colonization and lung aspiration).
- *Opportunistic infections* in immunocompromised patients or following organ transplantation.
- *Other infections* – Severe salmonella, Pl. falciparum or amoebic infection, fulminant tetanus, disseminated tuberculosis.

Causative organisms – Gram-negative and Gram-positive bacteria. Certain bacteria are associated with a particularly fulminating course. These include meningococcus (Waterhouse-Friderichsen syn.), Staph. aureus (toxic shock syndrome). Streptococcus pyogenes (streptococcal shock syndrome).

Staphylococcal toxic shock syndrome is a potentially fatal multisystem dysfunction and occurs primarily due to TSS toxin elaborated by *S. aureus.* It occurs in diverse settings often mimicking common febrile conditions.

Pathogenesis: TSS is considered to be a super-antigen mediated disease where *S. aureus* acts as a super-antigen. These super-antigens lead to a massive release of cytokines which are responsible for a capillary leak syndrome leading to clinical signs of TSS.

Risk factors for development Staph. TSS are tampon use vaginal colonization with toxin producing *S. aureus.* It has also occurred following use of nasal tampons for procedures of ears, nose and throat, cellulitis, subcutaneous abscesses, infected burns and pneumonia and viral infections such as varicella and influenza.

Cl. Fs.: Major criteria for diagnosis are: 1. Fever > 38.9°C. 2. Rash - Diffuse macular erythroderma. 3. Desquamation 1 to 2 weeks after onset of illness, particularly of palms and soles. 4. Hypotension.

Laboratory investigations – (a) Blood culture. Three sets must be obtained before starting antibiotic therapy. (b) Cultures from other sites of sepsis. (c) Others – Arterial blood gases and coagulation screen, CXR.

MANAGEMENT

(a) *Empirical antimicrobial therapy* (Table 83)

(b) *Treatment of source of infection*, e.g. drainage of abscesses.

(c) *Oxygen*. In septic shock patient is typically apnoeic and the hypoxaemia will not respond to inspired oxygen alone, indicating the need for artificial ventilation.

Table 83: Empirical antimicrobial therapy

Site of origin	*Antibiotic regimen*
Abdomen	3rd generation cephalosporins (ceftazidime, cefoperazone) + gentamicin + metronidazole.
Pneumonia	3rd generation cephalosporin with aminoglycoside
Neutropenia	Ticarcillin with clavulanic acid + aminoglycoside. If it persists add vancomycin. Possibility of fungal infection if no response.
Unknown source	3rd generation cephalosporin + ciprofloxacin or gentamicin + metronidazole.
Hospital-acquired infection	3rd generation cephalosporin + aminoglycoside or ciprofloxacin

Table 84: Common stimuli for anaphylaxis

1.	Antibiotics: Penicillin, streptomycin, tetracycline.
2.	Radio contrast media.
3.	Anaesthetic agents: Lignocaine, thiopentone, scoline.
4.	Blood and blood products including sera.
5.	Hormones: Insulin, growth hormone.
6.	Venoms: Bees, wasps, spiders.
7.	Others: NSAIDs, narcotic agents, heparin, thrombolytic agents, parenteral iron dextran, foods such as shellfish, eggs.

(d) *Correction of acidosis*: The acidosis will usually resolve as treatment of underlying disease is instituted.
(e) *Fluid replacement*: Usually initiated with a colloid followed by crystalloid.
(f) *Inotropic* support for maintaining BP and reducing the risk of complications such as acute tubular necrosis.
(g) *Nutrition*.
(h) **Anaphylactic shock:** Anaphylaxis is an acute and dramatic life-threatening immunological reaction to a drug or other stimulus (Table 84).

Clinical features – Onset may be instantaneous or within a few minutes after IV injection or at times after 1/2 hr after exposure. (a) Hypotension and circulatory collapse. (b) Severe laryngeal oedema/obstruction, angioedema, bronchospasm or pulmonary oedema may occur singly or in combination. (c) Tachycardia, arrhythmia, syncope and seizures on occasions constitute predominant presentation. (d) Diaphoresis, abdominal pain and diarrhoea may occur. (e) Urticaria may or may not occur.

MANAGEMENT

1. *Airway*: Intubation or if it is not possible secure emergency airway by puncturing the cricothyroid membrane with a large bore needle. Perform tracheostomy if intubation is not possible.
2. *Oxygen in high concentration*.
3. *Inj adrenaline* 0.5–1 mL of 1:1000 solution IM. Repeat every 5–10 mins if necessary. If no response or bronchospasm or cardiovascular collapse 5-–0 mL of 1:10000 solution IV, or instil it through endotracheal tube.
4. *Fluid* – 1/2-1 litre of fluid usually restores BP but 6–9 L may be required for adequate restoration of fluid volume.
5. *Hydrocortisone* – 300 mg IV followed by 100 mg q6h to prevent late manifestations of anaphylaxis.
6. *Aminophylline* – 250 mg IV in 20 mL dextrose to relieve bronchospasm.
7. *Diphenhydramine* – 50 mg (1 mg/kg) IV slowly repeated if necessary.
8. *Dopamine* if hypotension persists. 5 μg/kg/min increased to 10–20 μg/kg/min. If ineffective infusion of adrenaline 3–4 μg/min initially slowly increased till rise in BP.
9. *IV atropine and glucagon* if patient on β-blocker failing to respond.
10. *Ventilatory support* –may be necessary if patient is critical. In absence of airway obstruction there is little or no role of tracheal intubation in patients who do not require ventilation. Leaving an endotracheal tube in situ and allowing spontaneous breathing serves no useful purpose as excess secretions are rarely a problem in drug associated emergencies. The tracheal tube increases the work of breathing and is uncomfortable to the conscious patient.
5. **Vascular shock** – Due to impeded blood flow e.g. massive pulmonary embolism, dissecting aortic aneurysm, cardiac tamponade, ball valve thrombus of left atrium, tension pneumothorax.
6. **Endocrine shock** – (i) Severe hypopituitarism. (ii) Myxoedema. (iii) Acute adrenocortical insufficiency. (iv) Pheochromocytoma.
7. **Neurogenic** – Due to interruption of neural mechanisms that maintain vascular tone, cardiac output and venous return – General or spinal anaesthesia, wounds of pleura, testicular trauma.
8. **Drug-induced** – Ganglion blocking drugs, nitrates, poisoning with hypnotics.

13. HYPERTENSION

Hypertension in adults age 18 years and older is defined as systolic BP of 140 mm Hg or more and/or diastolic BP of 90 mmHg or more or any level of BP in patients taking antihypertensive medication.

Arterial pressure, like most physiological measures, is variable. Hypertension can be *primary or essential* when there is no obvious precipitating factor, or the much less common *secondary hypertension* where there is some identifiable cause.

WHEN TO SUSPECT HYPERTENSION

- Family history of hypertension
- Severe hypertension >80/110 mm Hg with onset at age <20 years or >50 years
- Difficult to treat or resistant hypertension with significant end organ damage features
- Combination of pain (headache), palpitation, pallor and perspiration 4 Ps of pheochromocytoma

Table 85: Classification of BP in adults as per JNC VII Criteria

BP classification	*SBP mm Hg*	*DPB mm Hg*
Normal	< 120	and < 80
Prehypertension	120-139	or 80-89
Stage 1 hypertension	140-159	or 90-99
Stage 2 hypertension	>160	or >100

- Polyuria, nocturia, proteinuria or hematuria indicative of renal disease
- Absence of peripheral pulses, brachiofemoral delay and abdominal or other peripheral vessel bruits
- History of polycystic kidney disease or palpable enlarged kidney
- Cushingoid features, multiple neurofibromatosis

CLASSIFICATION OF BP

Classification of BP in adults as per JNC VII Criteria is given in Table 85.

Causes and risk factors for secondary hypertension

See Table 86 for the causes of secondary hypertension, Table 87 for risk factors and Table 88 for Factors influencing risk of cardiovascular disease.

INVESTIGATION OF A CASE OF HYPERTENSION

I. Evaluation - Objectives:

- To identify known causes of hypertension
- To assess the presence or absence of target organ damage
- To identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide management

II. Medical history

- Duration and level of elevated BP, if known
- Symptoms of CAD, heart failure, cerebrovascular disease, peripheral vascular disease and CKD
- Diabetes mellitus, obesity, dyslipidaemia, gout, sexual dysfunction and other co-morbid conditions.
- Family history high BP, obesity, premature CAD and stroke, dyslipidaemia and diabetes
- Symptoms suggesting secondary causes of hypertension
- History of smoking or tobacco use, physical activity, dietary assessment including intake of sodium, alcohol, saturated fat and caffeine

Table 86: Causes of secondary hypertension

Renal	
Parenchymal	Acute and chronic glomerulonephritis
	Chronic kidney failure
	Pyelonephritis
	Polycystic disease
	Wilms' tumour
	Diabetes mellitus
	Gout with kidney failure
	Obstructive nephropathy
Arterial disease	Atherosclerosis
	Renal artery stenosis
	Polyarteritis nodosa
	Renal vasculitis
	Focal segmental sclerosis
Post-renal transplant patient	
Endocrine	
Adrenal cortical overactivity	Acromegaly
	Hypothyroidism
	Cushing's syndrome
	Conn's syndrome
	Congenital adrenal hyperplasia
Adrenal medullary overactivity	Pheochromocytoma
Cardiovascular	
Coarctation of aorta	
Middle aortic syn.	
Drug-induced	Steroids
	Oral contraceptives
	NSAIDs
	Phenylpropanolamine and analogues
	Cyclosporine
	Erythropoietin (sustained use)
	Sibutramine
Miscellaneous	Toxaemia of pregnancy
	Porphyria (during acute attacks)
	Lead poisoning (during acute phase)
	Raised intracranial pressure

- Socioeconomic status, professional and educational levels
- History of use intake of all prescribed and over-counter medication, illicit drugs, corticosteroids, NSAID, nasal drops. These may raise BP or interfere with effectiveness of antihypertensive drugs
- History of use of oral contraceptives and hypertension during pregnancy
- History of previous antihypertensive therapy, including adverse effects experienced, if any
- Psychological and environmental factors

PHYSICAL EXAMINATION

- Record 3 BP reading separated by 2 minutes, with patient either supine or sitting position and after standing for at least 2 minutes
- Examination of pulse and the extremities for delayed or absent femoral and peripheral arterial pulsations, bruits and pedal oedema
- Look for arcus senilis, acanthosis nigricans xanthelasma and xanthomas
- Examination of the neck for carotid murmurs, raised JVP or an enlarged thyroid gland
- Cardiac examination for location of apex beat, abnormalities of rate and rhythm, fourth heart sound and murmurs
- Examination of lungs for rales and rhonchi
- Abdominal examination for bruits, enlarged kidneys, masses and abnormal aortic pulsation
- Neurological assessment and optic fundus examination

Table 87: Risk factors for hypertension

Risk factor	*Comments*
Genetic factors	Familial hypertension
	Polygenic influence – Genes influencing renal function and sodium metabolism e.g. tendency for hypertensives to be 'salt sensitive' and normotensives to be 'salt-insensitive' may involve polymorphism mutation at renal tubule sodium transporters.
	Similarly angiotensinogen genotypes.
Race	Hypertension more common in blacks.
Age	Prevalence increases with age.
Obesity	Especially centripetal obesity.
Alcohol	Regular consumption of alcohol has a pressor effect.
Stress	Chronic psychological stress may lead to hypertension.
Drugs	NSAIDs, oral contraceptives, sympathomimetics
Metabolic	(Refer associated clinical condition)

LABORATORY AND OTHER INVESTIGATIONS

- *Routine*
  - Urine examination for protein and glucose and microscopic for RBCs and other sediments
  - Hb, fasting blood sugar, serum creatinine, total cholesterol and potassium
- Additional investigations in special circumstances
  - Fasting lipid profile and uric acid
  - Radiograph of chest
  - Echocardiogram
    - USG for renal sizes
    - Renal Doppler study to rule out renovascular disease
    - Fundus examination
    - Thyroid hormone profile and urinary metanephrine study in young patients

Table 88: Factors influencing risk of cardiovascular disease

RF for coronary artery disease	*Target organ damage (TOD)*	*Associated clinical conditions (ACC)*
• Age >55 years • Post-menopausal women • Smoking and tobacco use • Diabetes mellitus • Family history of premature CAD (males < 55, females < 65) • Increased waist hip ratio • Obesity and OSA • High LDL or total cholesterol • Low LDL cholesterol and high triglycerides • High sensitivity C-reactive Protein (hs-CRP) • Estimated GER <80 mL/min (MDRD) • Lipoproteinemia is a genetic risk factor	• LV hypertrophy detected by ECG and/or echocardiogram • Microalbuminuria/proteinuria and/or elevation of serum creatinine (1.2/2 mg/dL) • Urinary ACR (albumin-creatinine ratio) • Unilateral or radiological evidence of atherosclerotic plaques in the carotids • Hypertensive retinopathy	• Cerebrovascular disease • Ischaemic stroke • Cerebral hemorrhage • TIAs • Heart disease • Myocardial infarction • Angina • Coronary revascularization • CHF • Kidney disease • Diabetic nephropathy • Kidney failure (serum creatinine > 2 mg/dL) • Vascular disease: Peripheral arterial disease including non-specific aortoarteritis • Aortic dissection • Advanced hypertensive retinopathy • Haemorrhages or exudate • Papilloedema

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep. The devices used are either a microphone to measure Korotkoff sounds or a cuff that senses arterial waves using oscillometric techniques. *Indications* – Suspected white-coat hypertension and no target organ damage, apparent drug resistance, hypotensive symptoms with antihypertensive medication, episodic hypertension, autonomic dysfunction.

MANAGEMENT

I. **Lifestyle modifications** (Table 89)

II. **Pharmacological treatment**

Indications – (1) Malignant hypertension. (2) Hypertensive heart disease e.g. LVF. (3) Diastolic pressure 110 or more. (4) Males under 40 because the prognosis is poor if untreated. (5) Family history of early deaths due to hypertension. (6) Kidney failure with increase in serum creatinine (1.5 mg/dl).

See Table 90 for the antihypertensive agents.

Antihypertensive drug combinations

Not less than 15-20% of patients need more than two drugs to achieve goal BP

- Combination of drugs with different mechanisms of action are needed to achieve effective control of BP with minimal side effects. Combination of ACEIs with CCBs are advised
- Younger individuals have renin hypertension, hence ACE inhibitors/ARBs
- Older individuals have low renin hypertension, hence diuretics or CCBs are preferred as first line agents
- In combination, one out of two groups: ACE inhibitor/ARB or beta-blocker is combined with calcium channel blocker or thiazide diuretic.
- In refractory patients, when 3 agents are to be used ACE inhibitor or β-blocker combined with calcium channel blocker and thiazide diuretic is a good choice.

In diuretics chlorthalidone preferred over hydrochlorothiazide due to long action so once daily dose is sufficient but older patients need to be monitored for hyponatremia.

Undesirable combinations

- Low dose diuretics and calcium channel blockers
- Beta-blocker and ACE inhibitor
- Beta-blocker and verapamil/diltiazem
- ACE inhibitors and ARBs
- Two drugs from the same class

Drug interactions

- NSAIDs and COX-2 inhibitors decrease efficacy of diuretics, β-blockers and ACE inhibitors
- Concomitant use of β-blockers and non-dihydropyridine CCBs can result in heart blocks
- Cyclosporine levels are increased with diltiazem and verapamil
- Concomitant use of antidepressants with methyl dopa is to be avoided

III. **Symptomatic management**

1. **Hypertensive crisis** – comprises of:

A. ***Hypertensive emergencies*** – constitutes a group of clinical syndromes in which severe (DBP > 120) and rarely moderate hypertension is associated with established/ongoing target organ damage. Precipitating causes are listed in Table 91. Manifestations of hypertensive emergencies are listed in Table 92.

B. ***Hypertensive urgencies*** – The term is used when hypertensive crisis is not associated with target organ damage and include –

1. Accelerated malignant hypertension.
2. Atherothrombotic brain infarct with severe hypertension.
3. Rebound hypertension after sudden cessation of antihypertensive drugs.
4. Surgical: (a) Severe hypertension in patients requiring immediate surgery. (b) Postoperative hypertension. (c) Severe hypertension after kidney transplantation. (d) Severe body burns.
5. Grade I-II fundal changes.

Table 89: Lifestyle modifications

Intervention	*Recommendation*
• Wt. reduction	Maintain normal body wt.
• Adopt eating plan	Diet rich in fruits, vegetables and low-fat dairy products with reduced content of saturated and total fat
• Dietary sodium	Dietary sodium intake not more than reduction 2.4 g sodium or 6 g sodium chloride
• Physical activity	Regular physical activity such as brisk walking (at least 30 minutes per day, most days of the week)
• Moderation of alcohol	No more than 2 drinks (e.g. 24 oz beer, 10 oz wine, or 3 oz whiskey per day consumption in men, and no more than one drink per day in women)
• No smoking	
• Yoga, meditation and biofeedback	

Table 90: Antihypertensive drugs

Class of drugs	*Dosages*	*Indications*		*Contraindications*		*Adverse Reactions*
		Definite	*Possible*	*Definite*	*Relative*	
I. First Line Drugs						
Diuretics						
Hydrochlorothiazide Chlorthalidone Indapamide Amiloride Triamterene Spironolactone	6.25-25 12.5-25 1.5-2.5 5-10 50-100 25-50	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout		High doses can cause increase in serum cholesterol and triglycerides. Also glucose intolerance, hyperuricemia (gout), increased blood viscosity. Impotence.
Beta-blockers						
Metoprolol Bisoprolol Nebivolol	25.100 2.5-10 2.5-5	Angina Post MI Tachyarrhythmias Heart failure	Pregnancy diabetes	Asthma and COPD A-V block grade 2, 3	Dyslipidaemia Peripheral vascular disease Age >50 years	Bronchospasm, bradycardia, may mask insulin induced hypoglycaemia Impaired peripheral circulation, fatigue, decreased exercise tolerance.
Combined α and β-blockers						
Carvedilol Labetalol	6.25-50 200-400					Impotence Dyslipidaemia Hyperglycaemia
CCBs						
Amlodipine Diltiazem Verapamil S-amlodipine (racemic isomers)	2.5-10 90-360 80-240 2.5-10	Angina Elderly systolic hypertension Diabetes	CVA	Pregnancy Lactation Bil. renal artery stenosis	Moderate kidney failure Creatinine >3 mg/dL	Oedema of ankle Flushing Headache
ACE-inhibitors						
Enalapril Lisinopril Ramipril Perindopril Quinapril	2.5-20 2.5-20 1.25-10 2-8 10-80	Heart failure LV dysfunction Post MI Proteinuria (significant) Diabetes	CVA	Pregnancy Lactation		Cough Hyperkalaemia
ARBs						
Losartan Candesartan Valsartan Irbesartan Telmisartan Olmesartan	50-100 8-32 40-160 150-300 40-160 20-40	DM Proteinuria LV dysfunction ACE-inhibitor induced cough	Heart failure CVA	Pregnancy Lactation Bilateral renal artery stenosis Hyperkalaemia	Moderate kidney failure (creatinine >3 mg/dL)	Headache Dizziness Hyperkalaemia
II. Other drugs						
Alpha-blockers						
Prazosin Doxazosin	2.5-10 1-4	Prostatic hypertrophy CKD	Glucose intolerance Dyslipidemia		Orthostatic hypotension CHF	Postural hypotension

Contd...

Contd...

Class of drugs	*Dosages*	*Indications*		*Contraindications*		*Adverse Reactions*
		Definite	*Possible*	*Definite*	*Relative*	
Centrally acting agents						
Clonidine	0.1-0.3	Resistant hypertension	CKF	Pregnancy Lactation		Headache, sedation, dry mouth
Methyldopa	50-100	Hypertension in pregnancy	CKF	Pregnancy Lactation		Rebound hypertension
Minoxidine	0.2-0.4					Headache, sedation, postural hypotension
Vasodilators						
Hydralazine Minoxidil	25-150 2.5-80	Resistant hypertension Hypertension in pregnancy			CAD	Postural hypertension, tachycardia, fluid retention Lupus syndrome Hypertrichosis
Direct renin inhibitors						
Aliskiren	150-300	Resistant hypertension		Pregnancy Lactation Bilateral renal artery stenosis Hyperkalaemia	Moderate kidney failure (creatinine >3 mg/dL)	Angioedema Hyperkalaemia Diarrhoea

Table 91: Precipitating causes of hypertensive emergencies

- Non-compliance to therapy
- Abrupt drug withdrawal
- Acute renal disease
- Acute nervous system events
- Catecholamine excess e.g. pheochromocytoma
- Alcohol
- Drugs – Steroids, sympathomimetics
- Post-infarction coronary artery bypass

Table 92: Manifestations of hypertensive emergencies

1.	*End-organ damage*
	(a) Cerebrovascular – Hypertensive encephalopathy, ischaemic stroke, haemorrhagic stroke.
	(b) Cardiovascular – Acute LVF, acute aortic dissection, unstable angina.
	(c) Renal – Kidney failure.
2.	*Catecholamine excess syndrome* – Pheochromocytoma, clonidine withdrawal, monoamine oxidase inhibitor.
3.	*Post-operative bleeding from suture sites.*
4.	*Eclampsia.*
5.	*Severe epistaxis.*
6.	*Grade III-IV fundal changes.*

MANAGEMENT

1. Hospitalization
2. Immediate reduction of BP. Parenteral and oral drugs used in hypertensive crisis are listed in Tables 93 and 94, respectively.
3. Epistaxis – Nose packed with absorbent cotton soaked in adrenaline solution, cauterization after active bleeding has stopped or pressure fails to control bleeding. Nasal cavity pack if source of bleeding not accessible to cauterization.
4. LV failure – (Refer).
5. Cerebral haemorrhage – Rapid reduction of pressure to prevent further bleeding.
6. Dissecting aneurysm – Rapid reduction of BP. Propranolol may be useful.

IV. **Surgical treatment**

1. *Renovascular hypertension. Indications for surgery*– (a) Age 30 years or less. (b) Severe hypertension. (c) BP difficult to control medically. (d) Progressive kidney failure in a hypertensive patient is due to either bilateral renal stenosis or stenosis of the artery to a single kidney. Procedures – (a) Bypass grafting of renal artery. (b) Percutaneous transluminal angioplasty – (i) Fibromuscular dysplasia. (ii) Single discrete atheromatous plaque in renal arterial midportion. (iii) Intrarenal arterial stenosis inaccessible to surgery. (iv) Transplant artery stenosis. (v) Contraindication to surgery. Nephrectomy for unilateral contracted kidney due to ischaemia or chronic pyelonephritis.
2. *Surgery for coarctation of aorta.*
3. *Surgical removal of pheochromocytoma.*

Table 93: Parenteral drugs for hypertensive emergencies

Drug	*Dose*	*Onset of action Duration*	*Adverse effects*	*Special indications*
Vasodilators Sodium nitroprusside	0.25-10 µg/kg/ min as IV infusion	Immediate 1-2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies, caution with high intracranial pressure or azotaemia
Nicardipine hydrochloride	5-15 mg/IV	5-10 min 15-30 min, may exceed	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies, caution with IHD
Fenoldopam mesylate Nitroglycerin	0.1-0.3 µg/kg/min IV inf. 5-100 µg/ min IV inf.	4 h-6 min 36 min 2-5 min 5-10 min	Tachycardia, headache, nausea, flushing Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Most hypertensive emergencies, caution with glaucoma IHD
Enalaprilat	1.25-5mg q6h IV	15-30 min 6-12 h	Precipitous fall in BP in high-renin states; variable response	Acute LVF. Avoid in acute MI
Hydralazine hydrochloride	10-20 mg IV	10-20 min 1-4 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Adrenergic inhibitors				
Labetalol	20-80 mg IV bolus every 10 min 0.5-2 mg/min IV inf.	5-10 min 3-6 h	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol	25-50 µg/kg/min IV bolus, then 50 – 100 µg/kg/min by inf., may repeat bolus or increase inf. to 30 µg/min	1-2 min 10-30 min	Hypotension, nausea, asthma, heart block, HF	Aortic dissection, perioperative
Phentolamine	5-15 mg IV bolus	1-2 min 10-30 min	Tachycardia, flushing, headache	Catecholamine excess

Hypertension in Special Situations

Hypertension with DM

- Lifestyle modifications more aggressive
- ACE inhibitors first line drug therapy to reduce micro and macrovascular complications. ARBs if intolerance.
- β-blockers (cardioselective) if CAD and CHF. α-blockers can be used as useful adjunctive.
- Drugs useful in diabetic patients with hypertension - methyldopa, calcium channel blockers and labetalol. Use of diuretics during pregnancy can result in foetal growth/damage due to reduction in plasma volume.

Guidelines differ about target BP as newer studies have not shown benefit of contolling BP to <130/80 mm Hg as compared to <140/90 mm Hg.

Hypertension with Cerebrovascular Disease

- Immediately after an ischaemic cerebral infarction, treatment of high BP should be withheld unless it is very high. Cautious reduction by 10 to 15% only is suggested.
- In acute disease, goal is to gradually reduce BP and monitor it for first 24 hrs in view of possibility of transient hypertension.
- Hypertensive encephalopathy should be aggressively managed.
- BP should not be reduced in ischaemic stroke patients who are not for thrombolysis. In patients with thrombolytic therapy, SBP >185 and DSP >100 mm Hg should be treated and BP maintained below 185/130 mm Hg.

Table 94: Oral drugs for hypertensive urgencies to reduce diastolic pressure gradually over 24 hours

Drug	*Dose*	*Adverse Effects*
Nifedipine	10 mg. Repeat after 30 min	Tachycardia, headache, flushing
Captopril	25 mg Repeat every 30 min as required	Angioedema, rash, acute renal failure if bilateral renal stenosis
Clonidine	0.1-0.2 mg every hr. as required upto 0.7 mg	Drowsiness, sedation, dry mouth
Nimodipine*	60 mg q4h for 21 days	Hypotension, oedema, headache
Prazosin@	1-2 mg. Repeat after 1h if necessary	First dose syncope, orthostatic hypotension, palpitations, tachycardia, headache

* For SAH through naso-gastric tube in unconscious patient.
@Especially indicated for urgencies associated with increased circulating catecholamines.

Hypertension in Women

- Side effects like ACE inhibitors induced cough, CCB induced pedal oedema and diuretic induced hyperkalaemia are seen more often in women than in men.
- Oestrogen - progesterone oral contraceptives cause increase in SBP and to lesser extent DBP.
- Use of HRT (low dose oestrogen) in post-menopausal women is contraindicated.

Hypertension and pregnancy

- DBP >110 mm Hg needs urgent attention.
- Chronic hypertension is that which is present before pregnancy or that which persists 6 weeks postpartum.
- Pre-eclampsia superimposed on chronic hypertension is diagnosed when there is a further increase in BP of 30 mm Hg systolic or 15 mm Hg diastolic, together with proteinuria or oedema.
- Transient hypertension of pregnancy (gestational hypertension) is elevation of BP during pregnancy or during first 24 hrs postpartum with no other sign of pre-eclampsia or of pre-existing hypertension.
- Antihypertensive agent used should be safe to mother and foetus. Methyldopa for women whose hypertension is first diagnosed during pregnancy. Nifedipine, labetalol can be used.
- ACE inhibitors, ARBs and sodium nitroprusside are contraindicated. Use of low dose diuretics is discouraged, since pre-eclampsia is a volume-depleted state.
- Magnesium sulphate IV is drug of choice for both prevention and treatment of seizures. IV hydralazine and labetalol are also effective.

Hypertension in the Elderly

- SBP is a better predictor of cardiovascular/cerebrovascular events, end-stage kidney disease as compared to DBP.
- Some older patients may have falsely high readings due to excessive vascular stiffness. Also as older patients are more likely to have orthostatic hypotension, BP should be measured in supine, sitting and standing position.
- Targets for BP control are <140/80 for those 55–79 years. However for those over 80, SBP of 150/90 mm Hg is acceptable.
- Low dose diuretics like hydrochlorothiazide or chlorthalidone are effective in lowering morbidity and mortality but risk of hyponatremia. These could be combined with ACE inhibitors CCBs are preferred Alpha blockers are preferred in those with BPH.

Isolated Systolic Hypertension

- BP <160 mmHg may be necessary with marked systolic hypertension, if symptoms of giddiness and light headedness when the BP is reduced to 140/90.
- Isolated systolic hypertension seen in old age, often successfully treated with life-style modification and long-acting calcium channel blockers.

Hypertension with CHF

- ACE inhibitors in patients with LV dysfunction due to hypertension.
- Low dose diuretics if associated with fluid retention.
- In patients stabilized with ACE inhibitors and low dose diuretics selective β-blockers and α-β-blocker like carvedilol may be used whenever indicated. These should be started in low doses and then gradually increased.
- Amlodipine is safe in patients with angina and LV failure, when added to ACE inhibitors, low dose diuretics and digoxin.

Hypertension with Atrial Fibrillation

- Increased LV mass and enlargement of LA have been identified as independent determinants of new onset AF. BP control is strictly required when anticoagulant is given because stroke and bleeding episodes are more frequent when SBP is >140 mm Hg.
- A history of AF and systolic heart failure is a specific indication for using β-blockers.

Hypertension with Chronic Obstructive Pulmonary Disease

- Precipitating factors such as systemic steroids, beta-agonists or nasal decongestants and stress should be looked into and modified.

- Amlodipine is relatively safe. α-blockers can be used as add-on therapy in patients with COPD.

Hypertension with CAD

- β-blockers and CCBs are drugs of first choice for angina in patients with CAD.
- Treatment with Amlodipine is associated with fewer hospitalizations for unstable angina.
- Verapamil and diltiazem reduce risk of developing MI following non-Q wave MI.
- Statins and aspirin in patients with associated CAD.

Hypertension with Dyslipidaemia

- Life style modifications of particular importance.
- Choice of anti-hypertensive agent should be made after considering the effect on profile that some of these drugs have.
- β-blockers without intrinsic sympathomimetic activity (ISA) may increase levels of triglycerides and reduce levels of LDL cholesterol.
- Despite these, they have been shown to reduce risk of sudden death, overall mortality and recurrent MI.
- Statins

Hypertension with Obesity and Metabolic Syndrome

Obesity is almost always accompanied by insulin resistance, hyperinsulinemia, impaired glucose tolerance and dyslipidaemia (Table 95). Also abnormal obesity is associated with sodium retention, endothelial dysfunction, microalbuminuria, LVH and elevated markers of inflammation.

- Essential HT is very frequently associated with a decrease in insulin sensitivity. This insulin resistance is very often associated with dyslipidaemia, metabolic syndrome or the insulin resistant syndrome.

Table 95: Diagnostic criteria for metabolic syndrome

Risk factor	*Defining level*
Waist circumference	
Men	>90 cm
Women	>80 cm
Triglycerides HDL-cholesterol	>150 mg/dL
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>130/ >85 mm Hg
Fasting glucose	>100 mg/dL

Diagnosis of metabolic syndrome requires three or more of the above risk determinants to be present.

- Life style modification (diet, exercise) is the cornerstone of management in obese individuals.
- Dyslipidaemia in these patients is characterised by high TC levels and low HDL levels. Such patients require fibrates for control of dyslipidaemia.
- OSA now considered a cause of secondary hypertension is closely associated with obesity.
- On the basis of their favorable metabolic profiles, it seems that ACE inhibitors, ARBs, CCBs and alpha-blockers can decrease BP without worsening the metabolic abnormalities. ACE inhibitors, low-dose diuretics and non-dihydropyridine CCBs are the drugs of first choice in this setting. Alpha-blockers have particular advantages in individuals with dyslipidaemia or glucose intolerance and may be considered as add-on agents.

RESISTANT HYPERTENSION

Resistant hypertension is defined as the failure to achieve goal blood pressure in patients who are adhe-ring to full doses of an appropriate 3-drug regimen that includes a diuretic. Causes of resistant hypertension are given in Table 96.

Management of Resistant HT

- More aggressive salt restriction.
- Elimination of drugs interfering with action of antihypertensive agents.
- Multiple drugs in high dosages if no secondary cause is found.
- Newer intervention based treatment modalities such as renal sympathetic denervation therapy and carotid baroreceptor stimulation therapy are under evaluation.

ORTHOSTATIC HYPOTENSION (OH)

Normally, standing is accompanied by a small increase in DBP and a small decrease in SBP when compared with supine values. OH is present when there is supine to standing BP decrease >20 mm Hg systolic or >10 mm Hg diastolic after 2–3 minutes of standing. There is more OH in diabetics.

Causes of OH – Severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and certain venodilator antihypertensive drugs, especially α-blockers and α–β-blockers. Diuretics and nitrates may further aggravate OH.

In treating older hypertensive patients, one must be aware of potential OH symptoms such as postural unsteadiness, dizziness or even fainting. Lying and standing BPs should be measured periodically in all hypertensives over age of 50.

Table 96: Causes of Resistant hypertension

- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- Drug-induced or other causes
  - Nonadherence
  - Inadequate doses
  - Inappropriate combinations
  - NSAIDs, cyclooxygenase 2 inhibitors
  - Cocaine, amphetamine, other illicit drugs
  - Sympathomimetics (decongestants, anorectics)
  - Oral contraceptive hormones
  - Adrenal steroid hormone
  - Cyclosporine and tacrolimus
  - Erythropoietin
  - Liquorice and cough syrups
- Associated conditions
  - Obesity
  - Excess alcohol intake
- Identifiable causes of hypertension
  - Chronic kidney disease
  - Coarctation of aorta
  - Non-specific aortoarteritis
  - Cushing syn., chronic steroid therapy
  - Obstructive uropathy
  - Pheochromocytoma
  - Primary aldosteronism
  - Renal vascular hypertension
  - OSA syndrome
  - Thyroid or parathyroid disease

14. HEART MUSCLE DISEASE

Heart muscle disease can be idiopathic, genetic or specific. The myocardium can be affected in most types of heart disease; however, the terms 'myocarditis' and cardiomyopathy usually apply to conditions that primarily affect the heart muscle.

Specific heart muscle disease has known causes and is often associated with general systemic disease (e.g. sarcoidosis, amyloidosis).

ACUTE MYOCARDITIS

Acute damage to heart muscle by an inflammatory process. Myocarditis may resolve completely or partially, or it may deteriorate into a dilated cardiomyopathy. Viral myocarditis is the most common form. Other causes of myocarditis are listed in Table 97.

Table 97: Causes of myocarditis

Cause	*Example*
• Infections Viral Bacterial Rickettsiae Parasitic Spirochaetal	Rubella, Coxsackie echoviruses, mumps, influenza, dengue, HIV, Hepatitis C Diphtheria, pneumococcal (rare) Chlamydia, Coxiella Toxoplasma, trypanosomiasis Leptospirosis
• Immune disorders	Serum sickness, hypersensitive reaction to drugs, wasp stings, Lyme disease, Kawasaki disease
• Acute rheumatic fever	
• Physical	Radiation, severe hypothermia
• Connective tissue disease	Systemic lupus erythematosus, scleroderma, PAN
• Drugs and poisons	Carbon monoxide

Clinical Features

Symptoms – Dyspnoea, fatigue and sometimes precordial discomfort especially if associated pericarditis. Skeletal muscle pains in viral myocarditis.

Signs

- Tachycardia disproportionate to fever.
- Distended neck veins.
- Cardiac enlargement.
- Hypotension.
- S_1 soft, atrial and ventricular gallop sounds if severe disease.
- Murmur of MR and/or TR.
- Signs of CHF.
- Pericardial rub, arrhythmia and pulmonary or systemic embolization may occur.

Investigations

1. *ECG* – ST-T changes, low voltage, conduction defects and arrhythmias.
2. *Chest radiograph* – Cardiomegaly with pulmonary congestion.
3. *Echocardiography* – Useful in identifying chamber size, ventricular function, and pericardial effusion initially and serially. Doppler studies can assess MR and/or TR.
4. *Microbiological* – if an infection is suspected, appropriate specimens should be sent for microbiological investigation.
5. *Cardiac biomarkers* – Elevated levels reflect extent of myocardial necrosis.

6. *Nuclear imaging* – may identify diffuse or focal myocardial necrosis or inflammation, but the findings are non-specific. Thallium-201 perfusion scintigraphy may be abnormal due to faulty myocyte uptake, mimicking myocardial infarction.
7. *Endomyocardial biopsy* – in the acute stage will distinguish whether an acute inflammatory process is present, as opposed to a 'burnt out' cardiomyopathy.

Management

1. *Supportive measures* – Bed rest, diuretics for failure, anti-arrhythmic drugs. Prophylactic demand pacemaker may be needed for AV block in diphtheria. Steroids in viral and rheumatic carditis.
2. *Specific therapy* – Antitoxin in diphtheria, antibiotics. Beta-blockers, e.g. metoprolol may be of benefit.
3. *Corticosteroids* – may be used, e.g. in rheumatic carditis.

II. CARDIOMYOPATHY

Aetiology

Interaction of genetic factors and environmental exposure to viral antigen are thought to be aetiology of cardiomyopathy (Table 98).

Classification of Cardiomyopathies

See Table 99.

Dilated Cardiomyopathy

Dilated cardiomyopathy is characterized by a dilated hypokinetic left ventricle in absence of valvular, coronary, hypertensive or systemic disease. Right ventricular dilatation develops later.

Table 98: Aetiology of cardiomyopathy

• Idiopathic
• Autosomal dominant in about 50%
• Sporadic cases arise from new mutations which can affect proteins involved in the regulation of contraction
• Linkage to one of 4 genes:
β-myosin heavy chain gene on chromosome 14
Cardiac troponin T on chromosome 1
α-tropomyosin on chromosome 15
Myosin binding protein C on chromosome 11
• Loeffler's endocarditis
• Endomyocardial fibrosis
• Familial – Some cases

Clinical Features

are usually those of LV failure. Other presentations include systemic or pulmonary embolism, onset of atrial fibrillation, ventricular arrhythmia on routine ECG, or a mitral regurgitation murmur.

Investigations

ECG – Intraventricular conduction defect, low voltage in standard leads, high voltage in chest leads, left atrial P waves.

Chest radiograph – usually shows minimal left atrial enlargement and pulmonary venous congestion.

Echocardiography – Dilated LV with global hypokinesia which may be more marked in some areas (multifocal hypokinesia). The left ventricular thickness is usually normal. Functional MR is common (Fig. 111).

Angiography – is performed to exclude coronary artery disease.

Table 99: Classification of cardiomyopathies

Type	*Features*
Dilated cardiomyopathy	Enlargement of the cavity of the ventricle Low ejection fraction
Hypertrophic cardiomyopathy	Thickening of the ventricular wall associated with a small cavity High ejection fraction
Restrictive cardiomyopathy	Stiff ventricle which restricts filling. Ejection fraction maintained

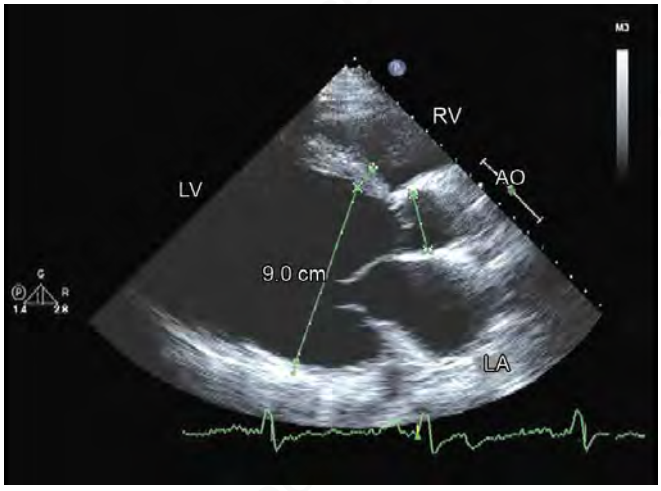


Fig. 111: 2D echocardiography in dilated cardiomyopathy sharing dilated LV

Management

Management is as for management of cardiac failure. Diuretics and ACE-inhibitors with addition of digoxin in advanced cases. Patients with atrial fibrillation require anticoagulant treatment. Antiarrhythmic drugs if symptomatic arrhythmias or when ectopic beats are so frequent as to cause hemodynamic deterioration.

Implanted defibrillator for any patient resuscitated from cardiac arrest and patients with recurrent ventricular tachycardia causing collapse or exacerbation of heart failure not controlled by antiarrhythmic drug treatment.

Cardiac transplantation offers long-term palliation for patients in NYHA class III or IV.

Special Forms of Dilated Cardiomyopathy

Postpartum cardiomyopathy is related to pregnancy. In worst cases, heart failure develops shortly after delivery, in milder cases symptoms occur later. Pregnancy seems to trigger an immunologically mediated myocarditis. Death may occur from overwhelming heart failure or patient may improve slowly.

Arrhythmic right ventricular cardiomyopathy (dysplasia) is inherited as an autosomal dominant condition with variable penetrance, gene defects have been matched to 14 and 1. It occurs in young males and is characterised by progressive fibro-adipose replacement of segments of the free wall of RV attributed to inappropriate focal myocyte apoptosis.

Patient may have family history of the condition or of sudden death during strenuous exercise. ECG may show inverted T waves in right precordial leads or RBBB. Epsilon wave in right-sided precordial leads. Focal or global RV dysfunction may be found on echocardiography.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as hypertrophy of the undilated left ventricle that cannot be explained by pressure or volume overload. The right ventricle is also hypertrophied.

Clinical Features

Symptoms

- Angina of effort
- Dyspnoea on effort
- Syncope
- Sudden death

Signs

- Jerky (rapid upstroke) pulse
- Palpable LV hypertrophy
- Bifid (double) apical impulse preceded by a presystolic impulse (due to LA hypertrophy)
- Systolic ejection murmur at the base
- Pansystolic murmur at apex due to MR
- Prominent 'a' waves in jugular pulse (from diminished RV compliance secondary to RV hypertrophy)

Investigations

X-ray – Heart usually not greatly enlarged, sometimes massive hypertrophy of LV.

ECG – LV hypertrophy, wide and double-peaked P waves suggesting LA hypertrophy. There may be large septal Q waves due to hypertrophy and fibrosis of the septum with a short PR interval and slurred upstroke of QRS resembling pre-excitation. Bizarre ECG changes are common.

2D-echocardiography – Obstruction in outflow tract, asymmetric septal hypertrophy (ASH), systolic movement of MV and early closure of AV (Figs. 112 to 114).

Colour Doppler ultrasound – detects LV outflow tract turbulence and when combined with continuous wave Doppler ultrasound, peak velocity of LV blood flow can be measured and LV gradients calculated.

Angiocardiography – Slit-like left ventricle with often starfish or banana appearance.

Management

(1) β-blocker, e.g. Propranolol 10 mg t.d.s. may be increased to 200 mg daily, useful especially for angina. Verapamil if propranolol ineffective. (2) Treatment of arrhythmias. For atrial fibrillation cardioversion may be necessary, under anticoagulant cover. (3) Antibiotic prophylaxis for IE. (4) Surgical treatment – Septal myomec-

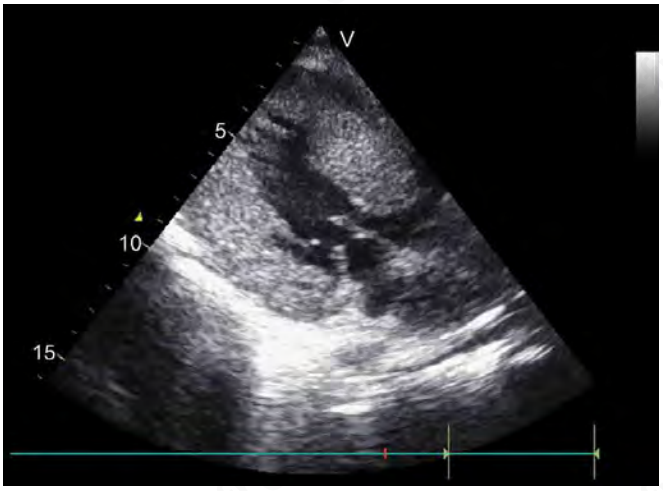


Fig. 112: 2D echo parasternal long axis view showing severe hypertrophy of interventricular septum and LV posterior wall

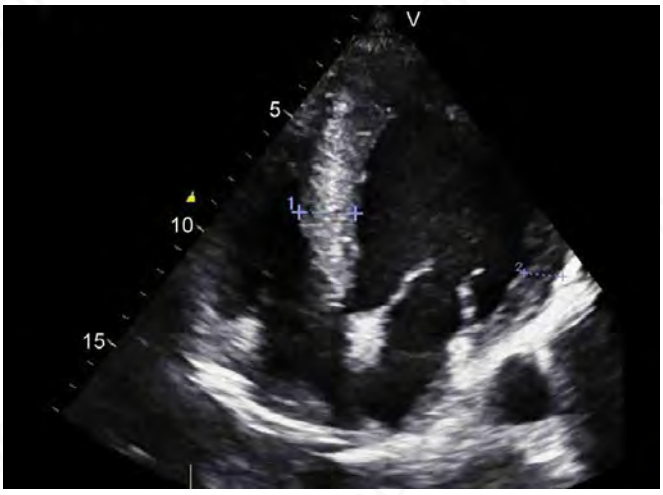


Fig. 113: 2D echo apical four-chamber view showing hypertrophied interventricular septum

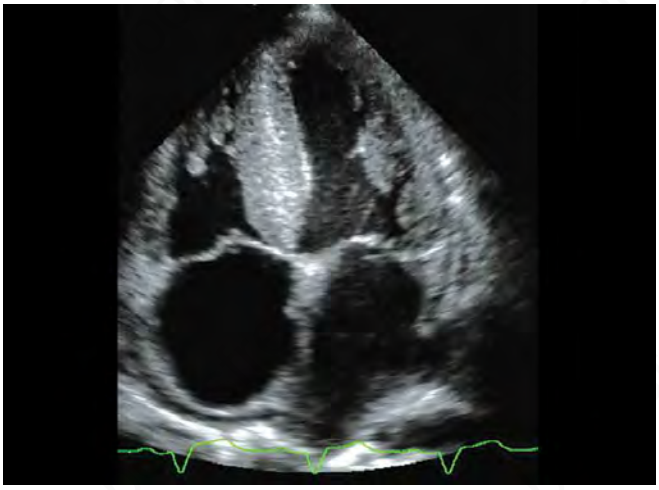


Fig. 114: 2D echo showing hyper trophied obstructive cardiomyopathy

tomy if refractory symptoms. Alternative to myomectomy is injection of 1 to 3 mL alcohol into major sepatal perforator coronary artery to create necrosis. If severe MR, mitral valve replacement. Cardiac transplantation may be considered in case of totally refractory symptoms and poor prognosis. (5) ICD insertion is considered in these patients with family history of sudden death, unexplained recent syncope, massive LV hypertrophy-wall thickness ≥ 30 mm, diffuse late gadolinium enhancement on MRI, hypotensive or attenuated blood pressure respond to exercise, multiple/repetitive nonsustained VT.

Restrictive (Obliterative) Cardiomyopathy

RC is impairment of ventricular filling by endocardial or myocardial disease or both.

Clinical Features

(a) *Right-sided disease* – Clinical picture resembles closely constrictive pericarditis with high central venous pressure, unimpressive ventricular pulsation and severe ascites without oedema.

(b) *Left-sided disease* – MR tends to occur mainly in early and mid-systole producing a decrescendo systolic murmur. Systemic emboli from thrombus in left ventricle may occur. Atrial fibrillation common.

Investigations

Chest radiograph – Enormous cardiac silhouette in right-sided disease due to giant right atrium, and partly due to an associated pericardial effusion. In left-sided form LV and LA are both enlarged. A linear strip of calcification may be seen in region of LV.

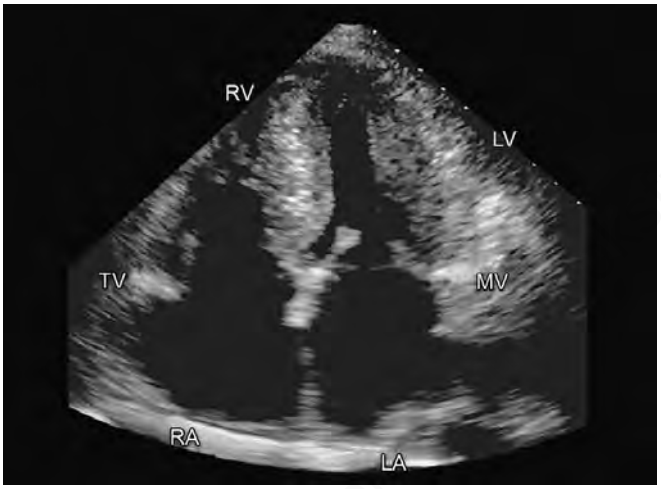


Fig. 115: 2D echo sharing thicked interventricular septum

Eosinophilia in blood common in EMF and Loeffler's endomyocardial disease.

ECG – Left atrial P waves. Low voltage QRS complexes usual.

Echocardiography – may show prominent bright echoes from increased endocardial collagen. Apical obliteration or thrombus, at times with calcium deposition is seen. Ventricular contractility is preserved and atrial dilatation is prominent. Doppler studies can define hemodynamic abnormalities, including diastolic MR and TR (Fig. 115).

MRI – may show prominent atrial signal in all phases of cardiac cycle, reflecting stasis of blood. It can define normal pericardial thickness and differentiate between constrictive pericarditis and RC.

Angiography – reveals mass of tissue in the ventricle, and in right-sided EMF giant RA. Ventricular cavity distortion by fibrosis and thrombosis helps in differentiation from constrictive pericarditis.

Endomyocardial biopsy – may help differentiate RC from constrictive pericarditis. It may help to diagnose one of the specific heart muscle diseases as the etiological factor.

Management

Drug therapy for CHF is mostly unsatisfactory. Anticoagulants for thromboembolic complications. Corticosteroids and immuno-suppressive drugs may help cases of EMF. Surgical resection of the obliterating endocardial tissue, with repair or replacement of regurgitant mitral and tricuspid valves can provide short-term benefit. Laser photoablation has been tried. Cardiac transplantation should be considered for end-stage disease.

Ischaemic Cardiomyopathy

Refers to a significant impairment of left ventricular function due to atherosclerotic coronary artery disease. This results in a dilated heart with symptoms and signs of intractable congestive heart failure. Thallium-201 perfusion scintigraphy demonstrates the defects and picks up the ischaemic myocardium even in the absence of angina. Positron emission tomography is useful in demonstrating ischaemic from idiopathic cardiomyopathy.

Peripartum cardiomyopathy as a diagnosis needs to be considered in antenatal and immediate postpartum, in women with clinical features of cardiac failure. It typically presents in last month of pregnancy and immediate postpartum.

Stress cardiomyopathy is a reversible form of acute cardiomyopathy that may mimic acute MI. LV contraction abnormality encompassing more than one coronary artery territory and no significant coronary stenosis on angiography.

Endocardial Fibroelastosis (EFE) – is an entirely different condition occurring in infants. It leads to early heart failure involving LV and is commonly associated with left sided congenital abnormalities such as AS and coarctation of aorta.

III. SPECIFIC HEART MUSCLE DISEASE

See Table 100 for various causes of heart muscle disease.

Table 100: Causes of heart muscle disease

- Infiltrations
  - Primary amyloid
  - Sarcoid
  - Hemochromatosis
  - Connective tissue disease
  - Systemic lupus erythematosus
  - Systemic sclerosis
  - Rheumatoid arthritis
  - Marfan's syndrome
- Endocrine and metabolic disorders
  - Diabetes
  - Acromegaly
  - Hypo-and hyperthyroidism
  - Glycogen storage disease
  - Carcinoid syndrome
  - Inherited storage diseases
- Drugs and toxins
  - Antineoplastic drugs
  - Alcohol
  - Irradiation
- Endomyocardial fibrosis and Loeffler's (hypereosinophilic) syndrome
- Neuromuscular disease
  - Friedreich's ataxia
  - Dystrophia myotonia

Clinical Features

1. Usual clinical picture like dilated cardiomyopathy (e.g. sarcoidosis, alcoholic heart disease, connective tissue disorders).
2. Clinical features resembling restrictive cardiomyopathy (e.g. amyloidosis and eosinophilic heart disease).
3. Mimicking hypertrophic cardiomyopathy (e.g. Friedreich's ataxia).

Scleroderma Cardiac Disease

Myocardial ischaemic fibrosis can occur in systemic sclerosis. It is due to microcirculatory impairment. Repeated focal ischaemic injury gives rise to irreversible myocardial fibrosis. Microvascular coronary vasospasm is known as "myocardial Raynaud's phenomenon".

IV. CARDIAC TUMOURS CARDIAC MYXOMAS

Left Atrial Myxomas

Intracardiac myxomas are the most common benign tumours of the heart and in majority are located in LA and rise from interatrial septum. Most common in women between 30 and 60 years of age.

Clinical features – Triad of

- Embolic phenomenon – Systemic emboli involving the brain, heart, extremities, kidney and aortic bifurcation.
- Systemic symptoms – Fever, anorexia, weight loss, myalgia, arthritis, Raynaud's phenomenon, petechiae and finger clubbing (due to immunological reactions to necrotizing tumour).
- Obstructive manifestations – Obstruction of mitral valve simulates mitral stenosis producing left heart failure. A ball-valve mechanism can produce recurrent pulmonary oedema or stenosis, which can lead to sudden death.

Signs

1. Loud S_1 and accentuated S_2.
2. "Tumour plop" – Early diastolic sound produced by prolapse of the tumour through mitral valve.
3. Apical diastolic or systolic murmur or both usually present. Changing murmurs due to varying mitral obstruction.

Investigations

2D-echo – is diagnostic and reveals location, origin, and movement of the tumour (Fig. 116).

Treatment – Surgical resection of the tumour together with portion of atrial septum from which it arises.

Right Atrial Myxomas

Right atrial myxomas—are rare.

Clinical manifestations – Features of systemic venous hypertension, prominent jugular 'a' waves, oedema, hepatomegaly and ascites. Signs – Loud early systolic sound at lower sternal border, and systolic and diastolic murmurs at tricuspid area. Echo is diagnostic.

Treatment – surgical removal.

15. NEUROCIRCULATORY ASTHENIA

Neurocirculatory asthenia (effort syndrome, soldier's heart or anxiety neurosis) is a condition of ill health of psychogenic or neurogenic origin characterised by a group of symptoms and a general incapacity in adjusting to physical or mental strain, especially in hypersensitive individuals who in extreme cases may show the condition more or less constantly with little or no provocation.

AETIOLOGY

(a) *Age* – Commonest in young adults. (b) *Sex* – 60% females. (c) *Heredity*– Sensitive nervous system in family members. (d) *Aggravating factors* – Nervous strain, physical overexertion, exhausting illness or infectious disease, pregnancy.

SYMPTOMS

1. *Chest pain* – Inframammary, pinching or stabbing and fleeting, or dull pain of prolonged duration usually located near the cardiac apex, sometimes substernal, bears no relation to effort, usually associated with fatigue. Pain may radiate down the left arm, more commonly down the outer side unlike angina. Area over left breast or apex sore to touch.
2. *Dyspnoea* – common. Sensation as if the breath cannot go through. Sighing respirations characteristic; irregular breathing.

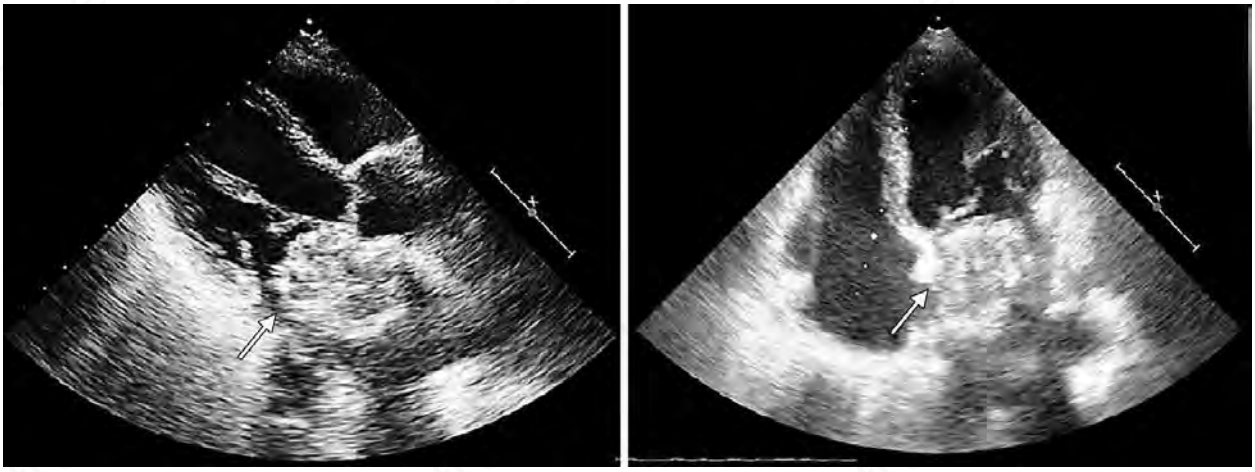


Fig. 116: 2D echo showing left atrial myxoma

3. *Palpitation* – particularly when lying on left side; often at night and at rest.
4. *Fatigue* – usually after waking in the morning, even after sound sleep. Exhaustion makes patient dread any activity.
5. *Fever* – of mild degree not uncommon. Temperature rarely more than 100.5°F and often detected after mild respiratory infection.
6. *Giddiness* – Usually light headedness or near blackout associated with sudden change of posture.
7. *Miscellaneous* – profuse perspiration, throbbing headache, trembling, irritability, flushing, insomnia, paraesthesia, diarrhoea, difficulty in concentration and mental and physical apathy.

SIGNS

None characteristic. Tachycardia, tachypnoea, sighing, tremors, moist cold palms and brisk tendon reflexes are often found as in nervous individuals. During a standard exercise test, these patients may have a lower oxygen consumption and greater rise in blood lactate than normal individuals. Slight elevation of blood pressure usually systolic.

PROGNOSIS

Good for life expectancy. Degree of incapacity depends on duration and intensity of symptoms. Outlook unfavourable if long history of symptoms, or syndrome precipitated after brief or minor strain and presence of significant psychomotor derangement. Recovery may occur after careful treatment but relapse also likely unless precipitating cause is discovered and abolished.

MANAGEMENT

i. Psychotherapy – Reassurance and explanation of non-organic nature of complaints. Identification of factors which aggravate symptoms. A depressive disorder as the cause of the cardiac symptoms should be excluded.

ii. Sedatives or tranquillizers may help.

16. PERICARDIAL DISEASE

PERICARDITIS

See Table 101 for the causes of pericarditis.

Table 101: Causes of pericarditis

- **Idiopathic** (*non-specific or benign*).
- **Myocardial infarction**
- **Infections**
  - Bacterial
  - Tuberculous.
  - Pyogenic – Intrathoracic infection, e.g. pneumonia, empyema, septicaemia or penetrating wounds of chest.
  - Viral – Coxsackie B, echovirus S, mumps, infectious mononucleosis, influenza, herpes simplex, HIV.
  - Fungal – Actinomycosis, histoplasmosis.
  - Protozoal – Amoebiasis, toxoplasmosis.
  - Parasitic – Echinococcus, cysticercus.
  - Spirochaetal – Syphilis, Lyme disease.
- **Metabolic**
  - Uraemia
  - Hypothyroidism
- **Autoimmune**
  - Rheumatic fever
  - Connective tissue diseases: Rheumatoid arthritis, SLE, scleroderma, polyarteritis nodosa, giant cell arteritis
- **Tumors and infiltrations**
  - Carcinoma bronchus or oesophagus, lymphoma, leukaemias
- **Delayed pericardial injury syndromes**
  - Post-pericardiotomy
  - Post-myocardial infarction (Dressler's syndrome)

Radiotherapy

- **Drugs** – Hydralazine. procainamide, methysergide, phenytoin
- **Haemopericardium**
  - Cardiac rupture
  - Aortic dissection
  - Trauma
  - Thoracic surgical procedures
  - Transvenous cardiac pacemaker

I. ACUTE PERICARDITIS

Symptoms

Onset – Abrupt with chills, fever and precordial pain, or insidious.

1. *Chest pain* – Main symptom. (i) Pleuritic pain aggravated by change of position, deep inspiration, coughing or swallowing. Sitting up and leaning forward may give relief. Radiation of pain to the trapezius ridge is nearly pathognomic. (ii) Steady severe pain simulating acute myocardial infarction.
2. *Dyspnoea and short hacking cough.*
3. *General symptoms* – Fever, sweating, chills, etc. depending on cause.

Signs

1. *Tachycardia.*
2. *Rapid respiratory rate.*
3. *Pericardial friction rub* – Superficial, scratching or grating to-and-fro sound localised to a small area over the precordium, the left sternal edge being the commonest site, or heard all over the left anterior chest. Three typical components – systolic, early diastolic, presystolic. May be transient for few hours or persist for many days. Seldom exactly the same in any two successive cardiac cycles, and changing from day to day.
4. *Atrial arrhythmias* – especially atrial fibrillation not uncommon.

EGG – (Figs. 117 and 118) Shows characteristic pattern due to injury to subepicardial portion of myocardium – Elevation of ST segments with an upward concavity particularly in leads I and II in acute stage, followed after 10–14 days by return of ST segments to iso-electric line with flattening or inversion of T waves. May be normal. PR segment depression is seen.

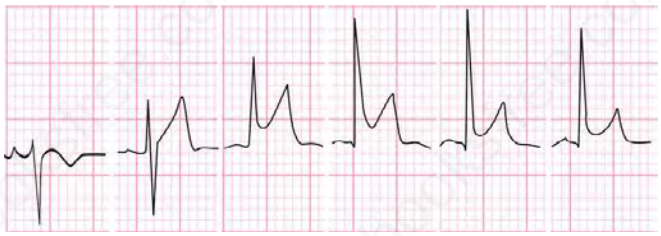


Fig. 117: Acute pericarditis. Concave ST segments elevation in all the leads facing the injured surface except aVR which faces the cavity of the heart

Treatment

(1) Bed rest. (2) Salicylates 2–6 gm/day and in severe cases other anti-inflammatory drugs such as indomethacin 100–200 mg/day or ibuprofen 600-1600 mg/day or prednisolone 20–60 mg/day. Initial high dose then rapid tapering protocol should be used for steroid therapy.(3) Colchicine 2–6 mg/day may help difficult cases.

II. PERICARDIAL EFFUSION

Types of Fluid

1. *Transudate*
   Congestive heart failure, Nephrotic syndrome, Myxoedema, Beriberi.
2. *Exudate*
   Serous – Usually tuberculosis, rarely acute benign pericarditis, or disseminated lupus erythematosus.
   Purulent – Haematogenous spread or direct from empyema, mediastinal abscess, amoebic liver abscess, or infection following aspiration.
3. *Haemorrhagic*
   Rupture of the ventricle in transmural myocardial infarction.
   Rupture of aortic dissection or of aneurysm of sinus of Valsalva into the pericardium.
   Tuberculous or malignant effusion. Thoracic trauma.
   Tear of right ventricle during pericardial puncture.

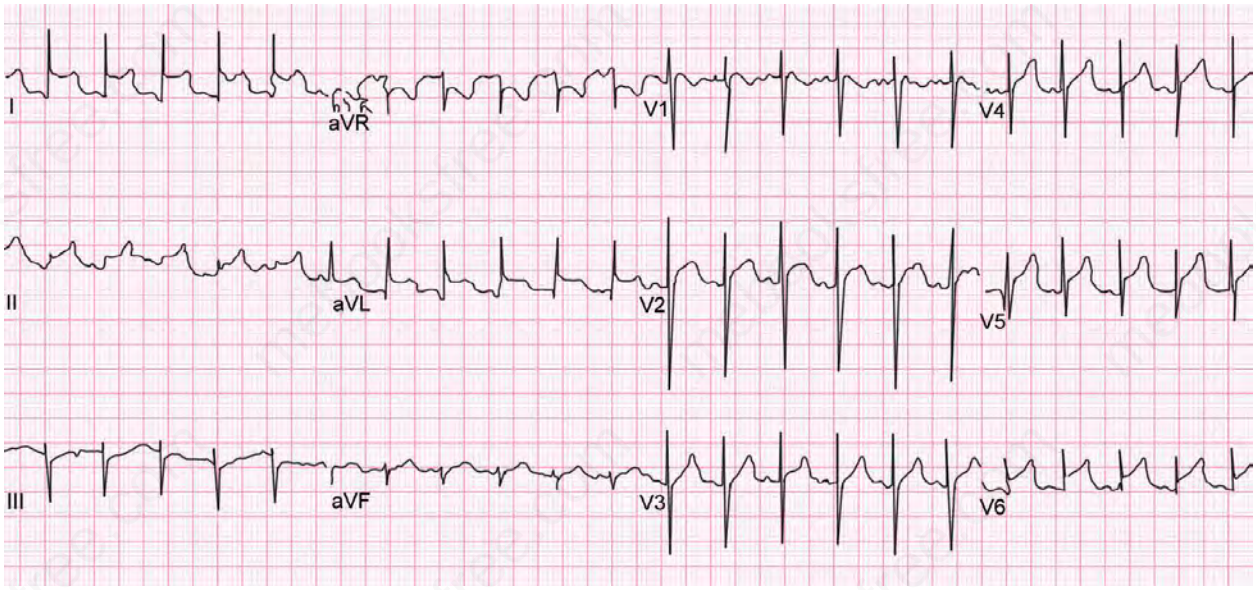


Fig. 118: 12-lead ECG acute pericarditis

Symptoms

1. Small effusion – No symptoms.
2. Large or rapidly developing effusion
   - ***Pain or precordial distress***

     Typical precordial pain – stabbing in character, worse with coughing, respiration, body movements and swallowing. Intensity varies from dull ache to severe pain. Usually, radiates to front of chest, may radiate widely to neck, arms and back.

     Dull heavy oppression due to distension of pericardial sac.

     Pain due to hepatic distension.
   - ***Symptoms due to compression*** – Pericardial effusion is accompanied by rise in intrapericardial pressure which if severe (*cardiac tamponade* Table 102) impairs venous return with consequent fall in cardiac output.

     Compression of heart resulting in insufficient blood to enter heart, lung and systemic arteries – Dyspnoea, faintness.

     Pressure of effusion on surrounding structures such as lungs, trachea, bronchi, oesophagus and great vessels – more dyspnoea or orthopnoea, pain, cough, hoarseness and dysphagia.
   - ***Constitutional symptoms*** – Fever, sweating, loss of weight, fatigue, etc.

Signs

Inspection – (1) Attitude – Bending forward or in the Mohammedan prayer position. (2) Bulging of precordium. (3) Apex beat not visible. (4) Jugular venous pressure elevated, y-descent is absent and inspiratory decrease in venous pressure is retained so Kussmaul sign is absent.

Table 102: Cardiac tamponade

Acute onset	
1.	Diagnostic CTVS procedures
2.	Aortic dissection (acute)
3.	Viral pericarditis
4.	Anticoagulant therapy
Slow onset	
1.	Tuberculosis
2.	Chronic kidney failure
3.	Post radiation
4.	Malignancy
5.	Rarely: Ca lung, breast, lymphomas, hypothyroidism, collagen vascular disorders, fungal infections

Palpation – (1) Apex beat feeble or not felt. (2) Pericardial rub may be felt. (3) Left lobe of liver often palpable.

Percussion – (1) Upper border of cardiac dullness in 2nd or 1st space when patient lies flat. (2) Dullness increased both to right and left. (3) Limit of dullness on left outside the apex impulse. (4) Flat percussion note over lower half of sternum (Dressler's sign). (5) Impairment of resonance in cardiohepatic angle (Rotch's sign).

Auscultation – (1) Heart sounds faint and muffled. (2) Pericardial friction rub may be heard. (3) Bronchial breathing and aegophony below angle of left scapula (Ewart's or Pin's sign). Usually attributed to collapse of the lung.

Pulse – Normal, small or pulsus paradoxus depending on the intrapericardial pressure. Pulsus paradoxus occurs when systolic pressure falls by 10 mm Hg or more on inspiration.

B.P.–With large effusion systolic pressure decreased and pulse pressure much diminished.

Beck's triad – hypotension, muffled heart sound and elevated jugular venous pressure.

Investigations

1. *Chest radiograph* (Fig. 119) – If effusion is large, water-bottle configuration in upright position, this becomes more globular in lying position. Straightening of cardiac border and widening of superior mediastinal shadow. Angle between right cardiac border and diaphragm more acute.
2. *ECG* – Low voltage of QRS complexes and T waves in all leads. With large effusion, a cyclical beat-to-beat pendular movement of the heart may produce electrical alternans.

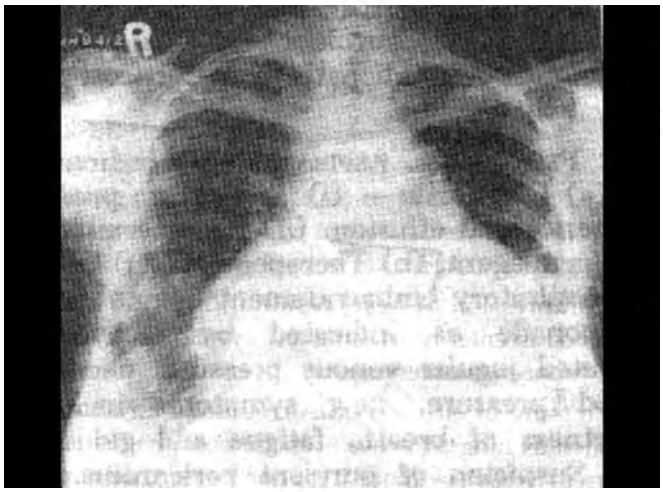


Fig. 119: Pericardial effusion. Leather-bottle or flask shape cardiac shadow. Other causes of such cardiomegaly are – Multiple valvular disease, Cardiomyopathy, ASD, Ebstein's anomaly

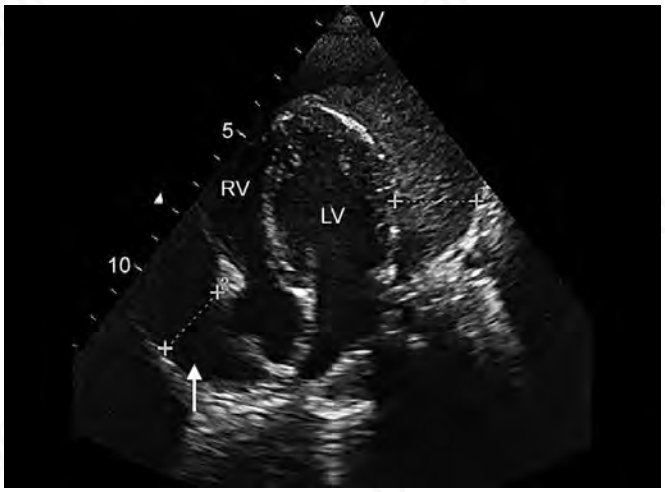


Fig. 120: 2D echo apical 4 chamber view showing large pericardial effusion (arrow)

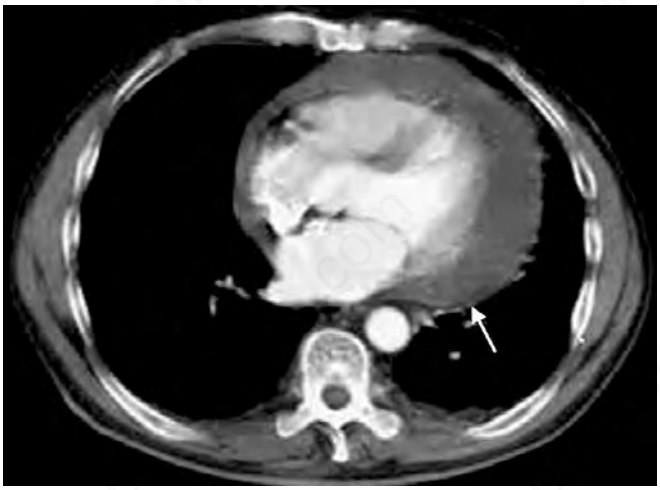


Fig. 121: CT chest shows pericardial effusion

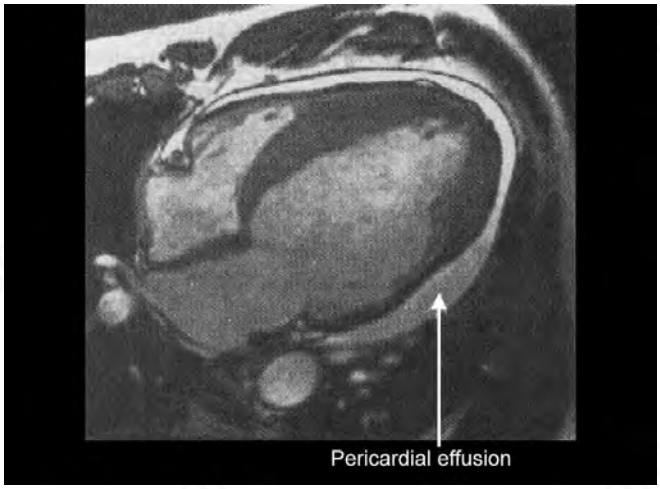


Fig. 122: MRI showing pericardial effusion

3. *Echo* – Echo-free space around the heart. Swinging of the heart. With tamponade RV compression with decreased diameters, RV indentation in late diastole, LA indentation, LV paradoxical motion of free wall, inspiratory pulsus paradoxus with RV expansion, shift of IV septum to left, decompression of LV, coarse oscillations of LV wall (Fig. 120).
4. *CT scan* – (Fig. 121)
5. *MRI* (Fig. 122) – If effusion difficult to see on echo (poor acoustic windows or echogenic effusion), the ability of MRI to freeze cardiac motion and to image in any plane can be an advantage. When effusion is due to pericardial malignancy or to disease in adjacent mediastinum, MRI can identify malignant tissue and high signal effusion (e.g. a haemorrhagic effusion).
6. *Pericardiocentesis* – may be diagnostic of the cause in some patients.

Management

1. Supportive Measures – Bed rest. Analgesics.
2. Of Underlying Cause – (a) Tuberculous effusion – Antituberculous therapy. (b) Rheumatic – Large doses of salicylates. Steroids if clinical evidence of associated carditis. (c) Purulent –Appropriate antibiotics. (d) Idiopathic – Corticosteroids may help.
3. Pericardial Aspiration

   Indications – (a) Diagnostic – (i) To confirm presence of pericardial effusion. (ii) To determine the etiologic agent.

   (b) Therapeutic – (i) Cardiac or respiratory embarrassment due to cardiac tamponade as indicated by tachycardia, elevated jugular venous pressure, decreased blood pressure, new symptoms including shortness of breath, fatigue and giddiness. (ii) Suspicion of purulent pericarditis. (iii) Tuberculosis.

   Preparation – The procedure is carried out under sterile conditions using local anaesthesia. Premedication is seldom required.

   Site – (a) Intercostal – is easier but carries risk of lung puncture or damage to coronary vessels if effusion is small. Also if fluid is pyogenic or malignant, the left pleural cavity may be contaminated. (b) Xiphoid – is less reliable but safer.

   Procedure – The chosen site is infiltrated with 1% lignocaine. A 10 cm 21 gauge needle is used for aspiration.

(a) Xiphoid approach – Patient should be propped up in bed at 45° to avoid entering the stomach. The needle is inserted about 3 cm below the xiphoid process at 30° to the skin pointing towards the patient's nose. If it strikes the costal margin, it should be withdrawn and reinstated at a deeper angle. When the needle surface is against the under surface of diaphragm, the syringe will move in and out with respiration. The needle should be introduced another about 2 cm until pericardial sac is entered. Monitoring of aspiration may be assisted by echo and/or recording ECG from the pericardiocentesis needle while performing the procedure; if the needle penetrates the heart, ECG shows an injury pattern. The needle is attached to a 2 mL syringe containing little saline. As the needle is slowly advanced, intermittent suction should be applied on the syringe. For diagnosis enough fluid can be drawn and collected for analysis. If a large amount of fluid is to be withdrawn, the narrow needle should be replaced by a 16 gauge catheter needle from an intravenous placement unit (or a lumbar puncture needle). The needle is connected to a three-way tap and 20 ml syringe. If there is difficulty in aspirating the fluid, it is quite safe with the flexible catheter in the sac to turn the patient on his side.

(b) Intercostal approach – is made in 5th or 6th left intercostal space in midclavicular line. The needle is inserted at right angles to the skin pointing slightly upwards. When the needle is on the left ventricle vigorous pulsations will be transmitted.

Complications – (i) Penetration of either ventricle. (ii) Laceration of coronary artery with formation of haemopericardium. (iii) Shock. (iv) Ventricular tachycardia.

Table 103: Causes of constrictive pericarditis

Common
• Tuberculosis in majority.
• Pyogenic pericarditis.
Rare
• Acute benign pericarditis.
• Following haemopericardium.
• Connective tissue diseases.
• Radiation therapy to chest.
• Uraemic.
• Idiopathic pericarditis.
• Rheumatoid arthritis.

4. Corticosteroids – In acute benign pericarditis, disseminated lupus, and pericarditis following myocardial infarction or pericardiotomy. Prednisolone 20 mg t.d.s.
5. Pericardiectomy – For chronic and recurrent pericardial effusion.

III. CONSTRICTIVE PERICARDITIS

Causes of constrictive pericarditis are listed in Table 103.

Clinical Features

A. ***Due to impaired filling of right side of heart***

Signs:

1. *Raised venous pressure* – and it may rise appreciably during inspiration (Kussmaul's sign). Sharp diastolic collapse ("y" descent) of venous pulse (Friedreich's sign) due to rapid inflow into the ventricles as the tricuspid valve opens with normal x-descent.
2. *Cardiac signs* – (a) Palpation – Apex impulse usually impalpable. Typically there is a systolic retraction of the apex beat which is followed by an abrupt outward movements as the ventricle fills rapidly in early diastole (diastolic shock). (b) Auscultation – Loud early 3rd sound (pericardial knock) due to checkrein mechanism and corresponding to the palpable diastolic shock. 2nd sound widely split with little variation with respiration. No heart murmurs or pericardial rub. Auscultation may be completely normal.
3. *Pulse* – Small and rapid. Pulsus paradoxus or atrial fibrillation may occur. Causes of absent pulsus paradoxus in constrictive pericarditis are listed in Table 104.
4. Hepatomegaly – Liver enlarged, tender but not pulsatile.
5. Ascites – occurs early with tendency to recur after tapping, and with little or no oedema of feet.
6. No orthopnoea.

Investigations

1. *Chest radiograph* – Triangular shaped heart with straightened right and left borders. Very little pulsation on fluoroscopy (quiet heart). Calcification of

Table 104: Causes of absent pulsus paradoxus in constrictive pericarditis

• LV dysfunction
• Positive pressure breathing
• Extreme hypotension
• Hypovolaemia
• Atrial septal defect
• Aortic regurgitation

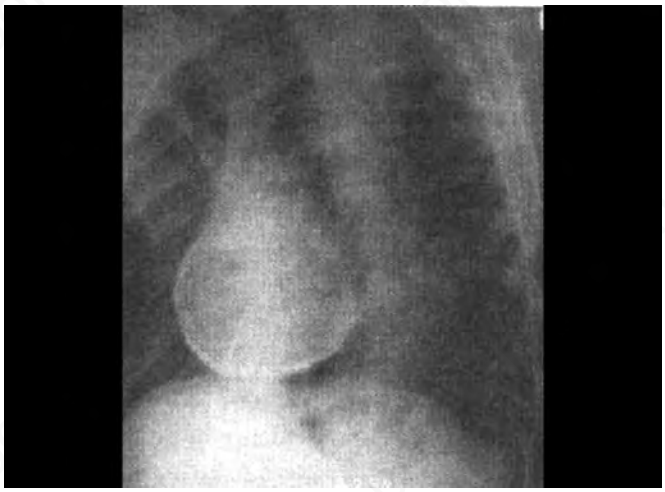


Fig. 123: Pericardial calcification in constrictive pericarditis

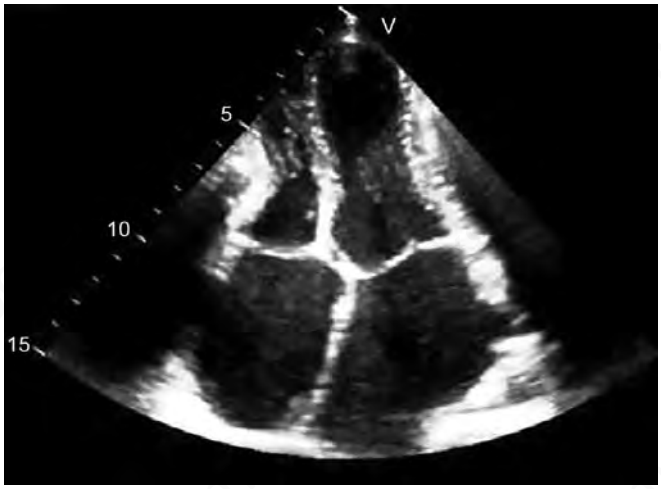


Fig. 125: 2D echo showing constrictive pericarditis

pericardium diagnostic (Fig. 123). A dilated superior vena cava is a valuable sign.

2. *ECG* – Low voltage with characteristic T terminal negativity (Fig. 124). There may be atrial fibrillation.
3. *Echocardiography* - (a) Small heart with good systolic function, or small ventricles and enlarged atria so that all the four cardiac chambers may be similar in size. (b) The pericardium is seen as single or double dense rigid shell surrounding the heart which is quite immobile (Fig. 125). (c) Abrupt displacement of interventricular septum during early diastole 'sepatal bounce' is seen. (d) The inferior vena cava and hepatic veins are grossly dilated and Doppler studies of aorta and pulmonary blood flow with blunted respiratory function confirm pulsus paradoxus. (In contrast patients with congestive cardiomyopathy show great ventricular dilatation with poor systolic contractility and pulsus alternans.) (e) Premature opening of pulmonary valve due to elevated RV early diastolic pressure.
4. *CT scan* – (Fig. 126)
5. *MRI* – can image thickened pericardium in any plane and is unaffected by calcification artefacts.

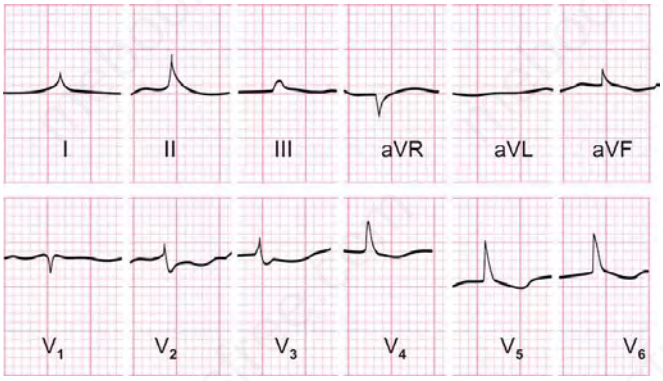


Fig. 124: Low voltage complexes in constrictive pericarditis

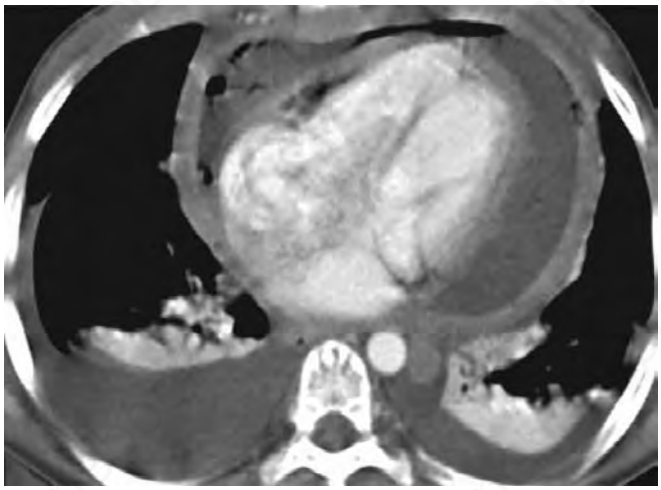


Fig. 126: CT chest shows pericardial effusion with few air pockets (postdrainage), the fluid thickness is up to 25 mm, outer layer of pericardium is thickened. Bilateral pleural effusion is present

Differential Diagnosis

1. *Restrictive cardiomyopathy* – Clinical features – No paradoxical pulse. JVP – Normal 'y' descent, no Kussmaul's sign. Prominent apical impulse. Often associated valvular incompetence. S3 low pitched. Investigations – X-ray – No pericardial calcification, cardiomegaly.

   ECG – LVH, intraventricular conduction disturbance. Echo – No pericardial thickening or effusion, LV thickening.

Catheter – LV end-diastolic pressure > RV end-diastolic pressure. Endomyocardial biopsy suggestive. Response to therapy – Reduction in height of JVP with diuretics.

2. *Cirrhosis of liver* – because of ascites, oedema. Jugular venous pressure normal or only slightly raised.
3. *Congestive cardiomyopathy* – Marked ventricular dilatation with poor systolic contractility and pulsus alternans.
4. *Tricuspid valve disease* – Systolic murmur of TR or diastolic murmur of TS.
5. *RV infarction* – Other features of IHD.

B. ***Due to impaired filling of left heart –*** Much less common. Patient presents with history of syncope on exertion with dyspnoea and evidence of pulmonary congestion.

Treatment

Pericardiectomy with removal of the thickened pericardium from the anterior surface of the heart. Course of antituberculous therapy even in absence of active tuberculous infection.

17. PULMONARY HYPERTENSION

A pathophysiological condition characterised by elevation of pressure in the pulmonary arterial system more than upper limit of normal, i.e. 30 mm Hg systolic, 15 mm diastolic, or 25 mm mean. Causes of pulmonary hypertension are given in Table 105.

Table 105: Causes of pulmonary hypertension

Primary or idiopathic
Secondary
• ***Passive*** – due to increase in resistance to left ventricular filling.
– Mitral stenosis.
– LV failure.
• ***Active or vasoconstrictive*** – due to
– Alveolar hypoxia.
– High altitude exposure.
• ***Obstructive or obliterative*** – due to increase in pulmonary vascular resistance.
Obstructive
– Miliary emboli or thrombi (in small pulmonary vessels) Veno-occlusive disease
Obliterative
– Chronic bronchitis and emphysema
– Severe lung fibrosis
– Systemic sclerosis
– Polyarteritis nodosa
– SLE
– Schistosomiasis
• ***Hyperkinetic*** – due to increased pulmonary arterial blood flow
– PDA
– ASD
– VSD
– Total anomalous pulmonary venous drainage
– Persistent truncus
– Transposition of great vessels
• ***Miscellaneous***
– Liver cirrhosis (from porto-systemic shunts)
– Sickle cell disease (due to repeated sickle crisis)
– Toxin-mediated (consumption of denatured rape seed oil)

PRIMARY PULMONARY HYPERTENSION

Symptoms

1. *Due to lowered cardiac output* – Easy fatigability, dizziness, syncopal attacks.
2. *Due to diminished coronary perfusion* – Angina-like chest pain due to RV ischaemia.

Signs

Inspection – Cyanosis usually peripheral, central cyanosis if foramen ovale becomes patent. Giant 'a' waves in jugular venous pulse.

Palpation – Left parasternal heave due to RV hypertrophy. Small arterial pulse and cold extremities. Diastolic shock in pulmonary area. Presystolic hepatic pulsation may be felt.

Auscultation –

Sounds – Narrow splitting of S_2 with increased intensity of pulmonary component, S_3 and/or S_4 gallop rhythms.

Murmurs – (a) Systolic ejection murmur due to blood flow through dilated pulmonary artery. (b) Early diastolic murmur of relative pulmonary regurgitation. (c) Pansystolic murmur of functional TR not uncommon.

Investigations

1. *ECG* – RV and often RA hypertrophy (P pulmonale).
2. Chest radiograph – Prominent main pulmonary arteries, but peripheral lung fields show slight decrease in vascular markings.

Special Diagnostic Evaluation:

(a) *Echocardiography* – Dilatation of RV and RA, paradoxical motion of ventricular septum and abnormal motion of pulmonary valve leaflets, inteventricular septal flattening, tricuspid regugitation suggestive of PH. May be evidence of underlying cardiac disease, e.g. MS. It provides estimate of pulmonary artery systolic pressure. LV systolic and diastolic function, detects systemic to pulmonary shunt.

(b) *Cardiac catheterization* – Allows direct measurement of pulmonary artery pressure and capillary wedge pressure which is elevated if PH is due to left-sided heart disease.

(c) *Arterial blood gases* – May show arterial hypoxaemia.

(d) *Pulmonary function tests* – Hypoxia due to ventilation-perfusion mismatch and reduced gas transfer.

(e) *Ventilation-perfusion lung scans* – May reveal evidence of pulmonary thromboembolism.

(f) *High-resolution CT* of chest to exclude occult interstitial lung disease.

(g) *High Helical CT* to detect pulmonary thromboembolism.

(h) *Lung biopsy* – for possibility of discovering a specific unsuspected cause, as well as assessing reversibility or irreversibility of vascular changes.

Differential Diagnosis

1. *'Damped' mitral stenosis* – High pulmonary vascular resistance with attacks of paroxysmal dyspnoea and pulmonary oedema. ECG shows P waves which are combination of P-mitrale and P-pulmonale.
2. *Eisenmenger complex* – History over many years, either sex, no giant 'a' waves, more central cyanosis rather than peripheral, pulmonary ejection murmur and thrill common. Angiocardiography shows bidirectional shunt.
3. *Chronic thromboembolic pulmonary hypertension* – Refer pulmonary embolism.

Management

(a) Of underlying cardiac or pulmonary disease if identified.

(b) Continuous anticoagulation for patients with recurrent pulmonary emboli.

(c) Calcium channel blocker such as nifedipine to alleviate pulmonary vasoconstriction.

(d) Chronic oxygen therapy especially at night, may be useful in patients whose pulmonary artery pressure is shown to decrease during oxygen inhalation, to alleviate pulmonary vasoconstriction.

(e) Other drugs
- Prostacyclin analogue
- Epoprostenol, a short acting vasodilator by IV infusion or Iloprost IV or via nasal route
- Endothelial-I receptor antagonist (Bosentan) 25–50 mg bd
- Selective phosphodiesterase - 5 inhibitor (sildenafil) 62.5 mg bd increasing to maintenance 125 mg bd
- Ambrisentan 5–10 mg bd

(f) Heart-lung transplantation has been attempted for far advanced cases.

PULMONARY VENOUS HYPERTENSION (PVH)

PVH is the principal disorder affecting pulmonary veins and is a common manifestation of adult heart disease (predominantly left-sided) (Table 106).

Chest Radiograph

As pulmonary venous pressure increases, radiographic signs, tend to occur in a sequence.

Interstitial oedema occurs with LA pressure of 22–30 cm H_2O. Vessels, particularly in the perihilar region and lower zones become hazy and ill-defined and airway walls thicken.

Septal (Kerley) lines appear. B lines are those most seen and are caused by oedema of interlobular septa. They are straight, short 1–2 cm, horizontal lines that touch the parietal pleura and occur commonly in the region of the costophrenic angle. Septal B lines can be distinguished from small vessels because they do not branch, touch the pleura and are dense for their width.

Laminar effusions are caused by fluid accumulation in the subvisceral pleural space, giving a band of soft-tissue density against the lateral chest wall in and just above the costophrenic angle.

Table 106: Causes of pulmonary venous hypertension

• Aortic valve disease
• LV disease: Ischaemia, reduced LV compliance (HCM)
• Mitral valve disease
• Left atrial myxoma
• Pulmonary venous obstruction (veno-occlusive disease)
• Heart failure with preserved ejection fraction

Alveolar oedema occurs when LA pressure exceeds 30 cm H_2O. Alveoli that have become filled with transudate become opaque (consolidation). Characteristically alveolar oedema is bilateral with a perihilar or lower zone predominance.

Management – treatment of underlying cause.

18. HEART DISEASE AND PREGNANCY

Normal circulatory changes in pregnancy:

1. *Blood volume* – increases gradually until term.
2. *Cardiac output* – rises by about 40% early in pregnancy and is maintained at this level up to term. After delivery, it generally returns to normal after 2 weeks.
3. *Venous pressure* – increases due to increase in blood volume.
4. *Arterial pressure* – Systolic pressure is unchanged but diastolic pressure falls giving wide pulse pressure.
5. *Regional blood flow* – Blood flow to skin and uterus gradually increases. Renal blood flow reaches maximum level in the first trimester and remains high thereafter.
6. *Pulse rate* – rises maximally between 8 and 10 weeks before delivery.

CARDIOVASCULAR MANIFESTATIONS DURING PREGNANCY

Symptoms

1. *Dyspnoea* – at rest or on exertion, may be related to hyperventilation. Orthopnoea especially in later months of pregnancy.
2. *Palpitation* – In mid and late pregnancy and puerperium. May be due to awareness of normal heart beat because of increased stroke volume or dysrhythmia.
3. *Oedema of legs* – during last 2 months due to increased venous pressure in legs, fluid retention, and reduced oncotic pressure of blood.
4. *Syncope* – in supine position because systolic pressure falls significantly due to pooling of blood in the legs.

Signs

1. *Apex beat* – displaced due to elevated diaphragm.
2. *Arterial pulse* – may be collapsing due to high stroke volume and low peripheral resistance.
3. *Heart sounds* – Loud mitral 1st sound and P2 due to forceful closure from increased stroke volume. 3rd heart sound often audible and may simulate gallop rhythm.
4. *Heart murmurs* – (a) Ejection systolic murmur at apex or base due to high stroke volume. (b) Late parasternal systolic murmur extending into diastole (mammary souffle) in late pregnancy and puerperium. (c) Flow murmur, e.g. mitral stenosis or aortic stenosis due to increased stroke volume. (d) Regurgitation murmur of MR and AR due to decreased peripheral resistance favouring forward flow.
5. *Raised JVP* – owing to high output state.
6. *Arrhythmias* – Ectopic beats, paroxysmal SVT.
7. *Hypotension* – is common due to vasodilatation, increased heat production and low resistance in uteroplacental circulation.
8. *Hypertension in pregnancy* – Causes of hypertension in pregnancy are given in Table 107.

ECG – Often prominent S waves in lead I, and Q waves with inverted T waves in III, due to rotation of heart.

Chest radiograph – Increased pulmonary shadows suggesting hilar congestion. Pulmonary arterial arc prominent due to increased blood flow.

MANAGEMENT OF CARDIAC DISEASE DURING PREGNANCY

Medical Management

1. *Restriction of activity* – More hours of rest and sleep.
2. *Infections* – Respiratory tract infections and pyelonephritis should be treated promptly.
3. *Arrhythmias* – Electrical cardioversion for atrial fibrillation. Quinidine should be avoided.
4. *Anaemia* – is not well tolerated and must be treated.
5. Antihypertensive drugs – See Table 108.
6. *Acute pulmonary oedema* – may be precipitated by anxiety and may even occur in a young patient with moderate MS and few symptoms prior to pregnancy. It is the commonest cause of cardiac death and should be treated promptly.
7. *Cyanotic attacks* – in cyanotic congenital heart disease may prove fatal to the mother as well as to the baby. They may respond to vasopressor drugs which increase systemic resistance, or propranolol which reduces right ventricular obstruction.
8. *Peripartal cardiomyopathy* – may lead to congestive failure in late pregnancy or puerperium especially in malnourished multiparous women (see cardiomyopathies).

Table 107: Causes of hypertension in pregnancy	
Chronic hypertension	BP >140 mm Hg or 90 mm Hg prior to pregnancy or before 20 weeks gestation Persists >12 weeks postpartum
Pre-eclampsia/eclampsia	BP >140 systolic or 90 diastolic with proteinuria (>300 mg/24 h) after 20 weeks gestation Can progress to eclampsia (seizures)
Chronic hypertension with superimposed pre-eclampsia	New onset proteinuria after 20 weeks in a woman with hypertension In a woman with hypertension and proteinuria prior to 20 weeks gestation Sudden 2 to 3-fold increase in proteinuria Sudden increase in BP Thrombocytopenia Elevated AST or ALT
Gestational hypertension	Hypertension without proteinuria occurring 20 weeks after gestation Temporary diagnosis May represent preproteinuric phase of pre-eclampsia or recurrence of chronic hypertension abated in midpregnancy May evolve to pre-eclampsia If severe, may result in higher rates of premature delivery and growth retardation than mild pre-eclampsia
HELLP syndrome	Peripheral smear showing evidence of haemolysis Elevated liver enzymes Low platelet count
Transient hypertension	Retrospective diagnosis BP normal by 12 weeks postpartum May recur in subsequent pregnancies Predictive of future systemic hypertension

(Refer hypertension in special situations)

Surgical Management

(a) *Mitral stenosis* – Mitral valvotomy preferably before 20th week if persistent pulmonary congestion despite adequate medical treatment. (b) *Congenital heart disease* – Surgical interference is seldom necessary during pregnancy.

Obstetric Management

Indications for Termination of Pregnancy

(1) *Cardiac failure – Before 14th week* – Left-sided failure if patient unsuitable for valvotomy, or CHF. *After 14th week* – LVF or CHF. If unsuitable for valvotomy, continuation of pregnancy unless deterioration.

(2) *Other factors* – (a) Atrial fibrillation – if persistent. (b) Primipara over 35, pregnancies in quick succession or associated other disease. (c) Hypertension – Continuing rise of blood pressure, or malignant hypertension. (d) Coronary heart disease. (e) Primary pulmonary hypertension. (f) Congenital heart disease – Eisenmenger's complex. Evidence of development of dissection in coarctation of aorta.

Management of Labour

(1) Second stage should be kept as short as possible with the use of forceps if needed. (2) Cardiac stress during labour is less if patient is kept on the side. (3) Oxygen and sedation with pentazocine should be used freely if patient is in distress. (4) Prophylaxis of bacteraemia and bacterial endocarditis with broad spectrum antibiotic at commencement of labour and then six-hourly for 48 hours.

19. PAROXYSMAL DYSPNOEA

Causes and Differential Diagnosis:

I. ***Cardiac conditions***

1. ***Cardiac asthma*** – (Table 109)
2. ***Acute myocardial infarction*** – Pain, dyspnoea, vomiting and shock. Cardiac signs and ECG changes.
3. ***Acute right ventricular failure*** – e.g. due to paroxysmal tachycardia, diphtheria, etc.
4. ***Mitral stenosis*** – Dyspnoea due to acute pulmonary congestion may follow severe exertion or excitement, infection or onset of atrial fibrillation. Diastolic murmur at apex.
5. ***Aortic regurgitation*** – Paroxysmal nocturnal dyspnoea often initial complaint. Cardiac and peripheral signs of aortic regurgitation.
6. ***Cardiac tamponade*** - Due to rapidly accumulating pericardial effusion or haemopericardium. Beck's triad of (a) falling arterial pressure, (b) rising venous pressure, (c) small quiet heart.

Table 108: Antihypertensive drugs in pregnancy

Drug	*Comments*
(a) *Chronic hypertension*	
• Methyldopa	Preferred for safety
• Beta-blockers	Reports of intrauterine growth retardation (atenolol)
• Labetalol	Increasingly preferred to methyldopa because of reduced side-effects
• Diuretics	Not first-line agents Probably safe
• ACEIs, ARBs	Contraindicated
	Reported foetal toxicity and death
• CCBs	May delay labour
(b) Acute severe hypertension in preeclampsia	
• Hydralazine	5 mg IV bolus, then 10 mg every 10-20 mins to maximum of 25 mg, repeat in several hrs. as necessary
• Labetalol (second line)	20 mg IV bolus, 40 mg 10 mins later, 80 mg every 20 mins.
• Sodium nitroprusside (rarely when others fail)	0.25 µg/kg/min to maximum of 5 µg/kg/min Foetal cyanide poisoning may occur if used for more than 4 hours.

II. ***Lung conditions***

1. ***Bronchial asthma*** – (Refer)
2. ***Acute bronchitis*** – Episodes of acute bronchitis with cough, sputum and breathlessness together with rhonchi, basal crackles and expiratory wheeze may occur in older patients. The differentiation from attacks of left heart failure resulting from ischaemic heart disease is often difficult as both may co-exist.
3. ***Spontaneous pneumothorax–*** Severe pain in chest, shock. Hyper-resonant note and shift of mediastinum.
4. ***Acute pulmonary oedema*** – Due to cause other than left ventricular failure. (Refer)
5. ***Pulmonary embolism*** – Dyspnoea, precordial pain or haemoptysis. Local chest wall tenderness in presence of pulmonary infarction. Pleural friction rub. Central cyanosis. Left parasternal heave. D-dimer test, spiral CT pulmonary angiography, perfusion scanning of lungs.

Table 109: Differences between cardiac and bronchial asthma

		Cardiac asthma	*Bronchial asthma*
1.	*Past history*	Of hypertension, aortic disease or IHD	Of previous attacks of asthma, or other allergic conditions
2.	*Age*	Onset usually after 40	Any age
3.	*Precipitating factor*	May be precipitated by exertion or acute myocardial infarction or hypertension	Trigger factors may be infection, non-specific irritants, external allergens, exercise or emotional factors
4.	*Symptoms*		
	(a) Cough	Cough and dyspnoea almost simultaneous.	Starts with dyspnoea.
		Pink frothy sputum which increases in intensity towards end of attack.	Expectoration of thick sticky sputum
	(b) Wheezing	Rare	Usual
	(c) Sweating	Prominent	Rare unless acute severe asthma
5.	*Signs*		
	(a) Inspection:		
	(i) Accessory ms. of respiration	Not active	Active
	(ii) Shape of chest	Normal	Emphysematous
	(iii) Respirations	Rapid and shallow	Rapid with prolonged expiration
	(b) Auscultation:		
	(i) Chest	Expiration not unduly prolonged	Expiration markedly prolonged
		Crackles more than rhonchi in early stages at lung bases, gradually ascending up with progress of the attack	Rhonchi more than crackles Signs diffuse all over the lungs
	(ii) Heart	A_2 may be loud	Normal A_2
		Left ventricular gallop	RV gallop late feature of severe bronchial asthma

Contd...

Contd...

		Cardiac asthma	*Bronchial asthma*
	(c) Pulse	Full and bounding, or pulsus alternans	Feeble and rapid
	(d) BP	Usually elevated	Normal or low
	(e) Extremities	Cold	Warm (with CO_2 retention)
	(f) Signs of underlying disease	AR, AS, hypertension, or IHD	No evidence of cardiovascular disease
6.	*Investigations:*		
	Beta-natriuretic peptide	Raised	Normal
	ECG	LV preponderance, acute MI or LBBB	Normal or RV preponderance Normal or hyperinflated lungs
	CXR	Hilae become hazy, 'bat's wing' shadowing if pulmonary oedema	Focal or segmental atelectasis due to mucus plugs

III. ***Laryngeal conditions***

Acute laryngeal obstruction due to – (1) Whooping cough. (2) Foreign body in larynx. (3) Retropharyngeal abscess. (4) Laryngismus stridulus. (5) Other causes of acute inspiratory dyspnoea with stridor.

IV. ***"Renal asthma"*** – History of kidney disease. Tiredness, weakness and dyspnoea due to uraemia and cardiac failure. Symptoms preceded by weeks or months of progressive lethargy, loss of libido and oligomenorrhoea or amenorrhoea. Oedema of feet common. Blood urea and creatinine increased.

V. ***Mediastinal conditions***

1. *Syphilitic aortitis and aneurysm* – Paroxysmal dyspnoea especially at night common (syphilitic asthma). Paramanubrial dullness. 2nd aortic sound loud. Dilatation of aorta on X-ray.
2. *Mediastinal tumours* – Mediastinal syndrome of dyspnoea, inspiratory stridor and paroxysmal cough. Hoarseness and dysphagia with often signs of pressure on arteries, veins and nerves. Usually patient prefers to lean forward. X-ray – shadow of growth.
3. *Acute mediastinitis* – May be acute onset. Symptoms of inflammation – fever, toxaemia and leucocytosis. Pressure symptoms – dyspnoea and paroxysmal or brassy cough and cyanosis. Tenderness over sternum, cervical or dorsal spine. Dilated veins. X-ray – accentuation and broadening of superior mediastinal shadows.

VI. **Miscellaneous**

1. *Hysterical overventilation* – Usually young female, in presence of audience. Absence of signs of organic disease.
2. *Laryngeal crisis of tabes* – Noisy breathing, cough and acute dyspnoea. Absent knee jerks, pupillary changes, ataxia.

VII. **Acute beriberi** – Rapid onset of oedema, palpitation and dyspnoea. Dilatation of heart, gallop rhythm. Scanty urine. Usually tender calves, and absent deep reflexes. ECG – Low amplitude of QRS complexes, tachycardia and prolongation of QT interval.

VIII. **Thyroid crisis** – Signs of thyrotoxicosis. Marked tachycardia or atrial fibrillation, waterhammer pulse and visible pulsations of vessels of neck.

IX. **Thymic asthma** – Usually in infants. Dyspnoea less when child held in arms and held up or forwards and worse when made to lie down. X-ray: May show enlarged thymus.

X. **Polyarteritis nodosa** – Transient lung infiltrations and hilar adenopathy with or without eosinophilia. Presenting symptom may be asthma. Other widespread manifestations – abdominal, renal, cardiac and neurological. Fever common.

20. DISEASES OF VESSELS

DISEASES OF AORTA AND ITS BRANCHES

1. Abdominal aneurysms are commonest aortic aneurysms and usually due to atheroma.

Symptoms – Stages

1. Symptomless enlargement.
2. Onset of symptoms due to stretching–Pain across lower abdomen and lower back. Palpable aneurysm is tender.
3. Leaking aneurysm – Sudden severe pain in abdomen, flank and back, with collapse, followed by partial recovery for few hours and then further episodes leading to death within a few days.
4. Ruptured aneurysm – Sudden catastrophe without warning, or after episodes of leakage.

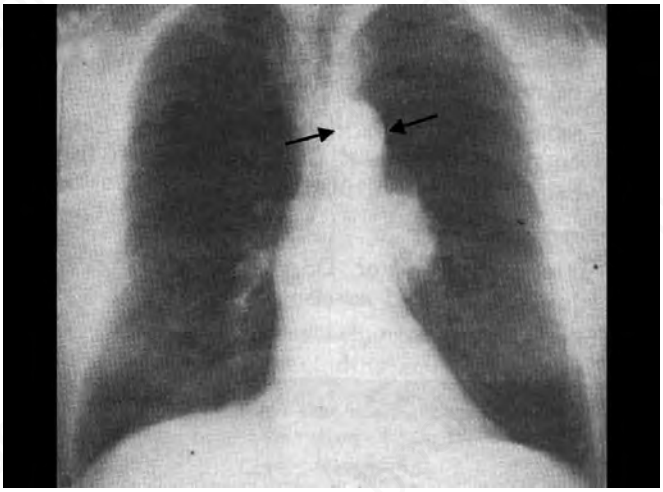


Fig.127: Chest radiograph showing: Atherosclerotic aortic aneurysm. There is localized prominence of the upper half of the descending aorta caused by widening of the aorta

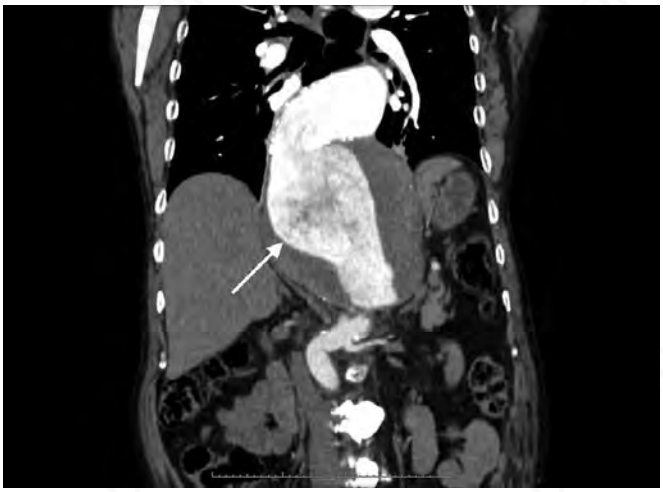


Fig. 128: MRI showing thoracoabdominal aneurysm with thrombus (arrow)

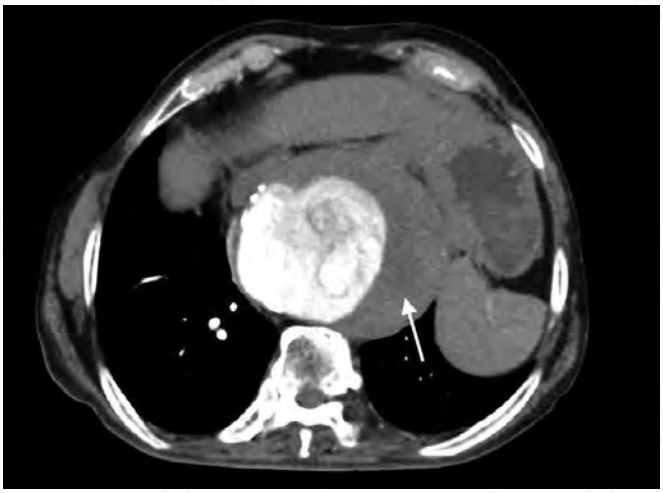


Fig. 129: MRI showing aortic aneurysm with thrombus (arrow)

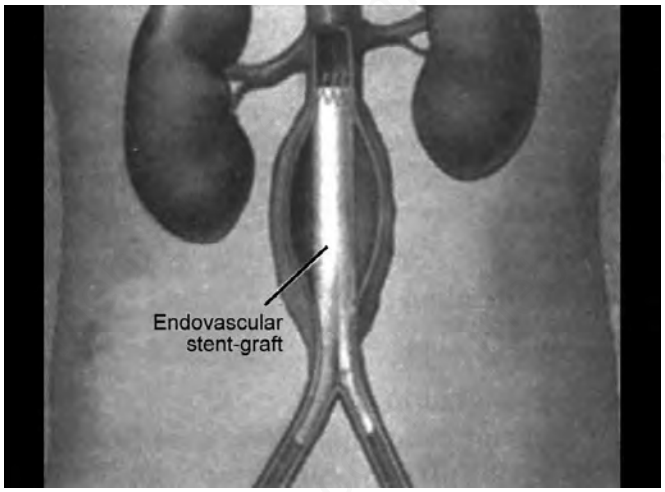


Fig. 130: Endovascular stent-graft

Investigations

1. *Chest Radiograph* (Fig. 127)
2. *Plain radiograph of abdomen* – in lateral position often shows calcification in the wall of the aorta or in the thrombus included in the sac.
3. *Aortography and/or DSA* – to determine size and extent of aneurysm.
4. *CT scanning* – useful not only for confirming diagnosis but also for determining the changes in size of aneurysm during follow-up periods.
5. *MRI* – can show full extent of aortic disease (Fig. 128).

2. **Thoracic aneurysms** involving ascending aorta, aortic arch and descending aorta are mostly due to atherosclerosis and now rarely due to syphilis. For clinical features, refer cardiovascular syphilis (Fig. 129).

   Management – Surgery is indicated for abdominal aortic aneurysms greater than 5.5 cm in diameter because of risk of rupture with Dacron tube or endovascular stenting considered (Fig. 130) and if stent – graft option limited and high surgical morbidity, elective surgery if aortic diameter exceeds 6 cm.

   In case of ascending aortic aneurysm, surgical replacement of aorta performed when ascending aortic

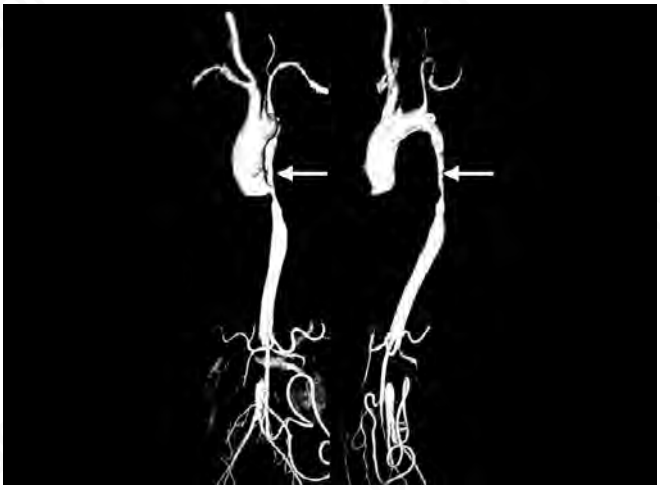


Fig. 131: MR angio showing narrowing of aorta due to aortoarteritis

diameter exceeds 5.5 cm and in setting of Marfan syndrome, bicuspid aortic valve, when it reaches 5 cm.

3. **Aortoarteritis** including both carotid arteries causes repeated syncope in young female (Fig. 131). This can be treated by replacing entire carotid arteries till the base of the skull with Dacron tube under hypothermia at 18° and circulatory arrest.
4. **Aortic dissection** – Usually in males over 50.

Classification (Stanford)

- Type A involving ascending aorta regardless of site of origin
- Type B involving descending aorta distal to the origin of left subclavian artery

Conditions associated with aortic dissection are listed in Table 110.

Clinical features – (a) Pain - Sudden onset of severe tearing pain in chest, often radiating through to the back, abdomen and thighs. Spread into the upper limbs, hand and neck may also occur if the lumen of the carotid and subclavian arteries is involved, and coronary insufficiency or infarction may occur due to dissection extending into either coronary artery. (b) Shock and prostration may be severe. (c) Absence or diminution of peripheral pulses – Weak, unequal or absent pulsations in carotid, radial and femoral arteries. (d) Hypertension in majority. (e) Death may occur from rupture into the pericardium.

Investigations

Chest radiograph – shows widening of mediastinum. If there is calcium in the aortic arch, its wide separation from the outer margin of aortic shadow is diagnostic.

Table 110: Conditions associated with aortic dissection

• Hypertension (in majority)
• Cystic medial degeneration
• Marfan's syndrome
• Ehlers-Danlos syndrome
• Previous surgery: Coronary bypass, replacement of aortic valve
• Pregnancy (usually third trimester)

ECG – LV hypertrophy but usually no ischaemic changes.

Echocardiography – may demonstrate a proximal ascending dissection, but transoesophageal echo can adequately demonstrate descending thoracic aorta. Transoesophageal colour Doppler can show the flow patterns to make the intimal tear more obvious.

MRI – demonstrates intraluminal thrombus and dissection flaps without the need for contrast medium and assesses severity of coexisting AR, periaortic hematoma and pericardial effusions.

Aortography or DSA – confirms diagnosis and outlines site of intimal tear.

CT scanning – with contrast enhancement. 1st choice of investigation.

Complications

Aortic regurgitation (developing for first time), obstruction of airways or oesophagus due to progressive obstruction of aorta.

Rupture of aorta resulting in pericardial or pleural effusion and occasionally intrabronchial hemorrhage which may result in death.

Management – (1) Admission to ICU. (2) Lowering of systolic pressure to around 100 mm Hg with sodium nitroprusside 50 mg in 250 mL of 5% dextrose (dose ranges from 0.5 to 6.0 mcg/kg/minute) or Propranolol 0.5–1 mg IV till adequate beta-blockade; can be repeated q6h, or methyldopa 250 mg IV or p.o. q6h may be combined with above drugs to maintain stable systolic BP (3) Measurement of arterial and venous pressures, and urinary output. (4) Surgery – Indications: (i) Urgent surgical consultation for all patients with thoracic aortic aneurysm and in life-threatening complication such as rupture in ascending aorta dissection. (ii) Presence of AR. (iii) Large haemorrhagic pleural effusion. (iv) Cardiac tamponade. (v) Hypertension not responding to drug therapy. (5) Medical therapy to be continued in type B dissection (tear distal to origin of left subclavian artery).

5. **Aortic arch syndrome** (middle aortic syndrome, pulseless disease, reversed coarctation, Takayasu's syndrome) is a panarteritis of aorta and its main branches and of pulmonary arteries.

   Etiology– (a) Age – 20–30. (b) Sex – Mostly females. (c) Cause unknown, probably tuberculous.

Clinical Features

1. *Cardiovascular* – Diminished or absent pulsations in vessels of neck, head and arms. Syncopal attacks. Tachycardia and ectopic beats. Exertional dyspnoea, cardiomegaly and signs of cardiac failure secondary to underlying IHD. Harsh systolic murmurs over stenosed segments of a vessel and soft flow murmurs over various anastomotic channels. Hypertension, AR and aortic aneurysm.
2. *Cerebrovascular* – Focal transient symptoms in the carotid or vertebral artery territory or persistent focal neurologic deficit.
3. *Trophic changes* – Loss of teeth and hair, ulceration of nose or lips, perforation of nasal septum or palate, cataracts or facial atrophy.
4. *Symptoms of intermittent claudication* – Easy fatiguability, coldness. paraesthesia, cramp-like pains if collateral circulation is inadequate.

Investigations

Angiography and/or DSA – Narrowing or occlusion of involved vessels.

ESR and leucocyte count elevated.

Differential diagnosis (Table 111)

Treatment– (i) Antituberculous drugs. (ii) Anticoagulants to prevent clotting. (iii) Surgical management depending on site of lesion – thrombo-endarterectomy, excision with graft replacement, or by-pass graft.

Table 111: Differentiating features between middle aortic syndrome and congenital coarctation

	Middle aortic syndrome	*Congenital coarctation*
Sex	Females predominate	Males predominate
Claudication	Marked	Uncommon
Bruit	Usually abdominal	Usually thoracic
Associated tuberculous lesion	Often	Rare
Rib notching	Rare	Usual
Aortography	Usually elongated narrow segment	Usually short narrow segment
Left subclavian involvement	Common	Very rare

6. **Subclavian steal syndrome** (Brachio-basilar insufficiency).

   Mechanism – The syndrome is due to obstruction to innominate artery or subclavian below the origin of the vertebral artery. The affected arm can only receive blood supply by reverse flow down the vertebral artery into the subclavian above the obstruction. The vertebral artery draws its blood supply from the opposite vertebral artery via their junction at the base of the basilar artery. This causes an interference with the flow of blood into the brainstem, and this is exaggerated by movements of the affected arm.

   Symptoms and Signs – (a) Episodes of transient vertebrobasilar ischaemia triggered off by movements of the involved arm. (b) Diminished or absent pulse in the arm, and ischaemic and trophic changes may occur. (c) A murmur may be audible at the root of the neck.

   Investigation – Arch arteriography may show occlusion of one or both subclavian arteries with retrograde flow in one or more vertebral arteries to the distal part of the subclavian artery.

   Management – Endarterectomy and arterioplasty of innominate or subclavian arteries (Subclavian to common carotid bypass). Percutaneous vascularization with stents (balloon expandable stents) can be used.

7. **Marfan's syndrome** – A hereditary disorder of connective tissue (abiotrophy) which affects both sexes and may be familial.

Clinical Features

(a) *Skeletal stigmata* – Slender body build, abnormal height with disproportionately long bones especially fingers (arachnodactyly), high arched palate; lax, loose ligaments with hypotonic muscles; spinal deformities, and thoracic cage deformities such as depressed sternum and pectus excavatum. (b) *Cardiovascular involvement* – Dilatation of aorta, dissecting aneurysm, aortic incompetence. (c) *Ocular abnormalities* – Dislocation of lens or myopia. (d) *Pulmonary disease* – Spontaneous pneumothorax, congenital cystic lung, congenital atelectasis.

Management – ARB – Losartan should be considered in patients with aortic root disease, stabilizes root size.

Peripheral Vascular Disease

PERIPHERAL ARTERIAL DISEASE (PAD)

PAD is a clinical term that denotes an occlusive disease arising from narrowing of the arteries distal to the arch of the aorta. Causes of peripheral arterial disease are enumerated in Table 112.

Atherosclerosis Obliterans

Risk factors – Main factors leading to progressive narrowing of the major arteries of the legs are smoking, hypertension, diabetes mellitus and hyperlipidaemia.

Symptoms

1. ***Intermittent claudication*** – Severe cramping pains or discomfort on walking which disappears after short rest and recurs when the walk is resumed. The symptom is due to inability of narrow arteries to provide additional blood supply necessary for the exercising muscles. The position of pain of claudication depends on the level of arterial lesion – (a) *Calf claudication* – usually due to obstruction in femoro-popliteal segment. (b) *Thigh claudication* – usually due to iliac occlusion with associated buttock claudications. (c) *Claudication of buttocks, thighs and calves* with impotency in males – Aortic bifurcation lesion.
2. ***Rest pain***– is less common and suggests more advanced disease. (a) *Pain due to acute arterial occlusion* – Severe pain in tissues distal to the site of obstruction aggravated by limb movement. (b) *Pain due to ischaemic neuropathy* – Severe burning or lancinating type of pain occurring usually in paroxysms and worse at night. (c) *Pain of pregangrene* – Burning, throbbing type of pain which may make the patient sit up in bed and hold his legs. Pain aggravated by heat.
3. ***Other symptoms***– Numbness and tingling and feeling of coldness in the involved extremity. The occurrence of sepsis in minor abrasions of the feet may be the first evidence of incipient ischaemia in the limb.

Table 112: Causes of peripheral arterial disease

- Due to arterial obstruction
  - *Degenerative disease of arteries* – Peripheral arteriosclerosis including arterial thrombosis (senile, diabetic) and embolism.
  - *Inflammatory diseases of arteries* – (i) Thromboangiitis obliterans. (ii) Infections – IE, tuberculosis, syphilis, typhoid fever. (iii) Arteritis – Polyarteritis nodosa, giant cell arteritis, Takayasu's disease, rheumatoid disease.
- Vasomotor
  - Vasoconstriction – Raynaud's disease, acrocyanosis, ergotism.
  - Vasodilation – Erythromelalgia.
- Due to physical and chemical agents
  - *Trauma* – Contusion, aneurysm, arteriovenous fistulae.
  - *Cold* – Chilblain, frost bite, trench foot and immersion foot.
  - *Chemical* – Phenol, ergot, thiopentone, lead.
- Due to arteriovenous communications.

Examination

(a) *Inspection* – of feet. In presence of rest pain, feet and toes will be cold with purple or bluish discolouration. In more advanced cases (pregangrene) atrophic skin, poor colour and sluggish capillary circulation.

(b) *Palpation* – (i) Absence of pulses below the femoral pulse (femoral artery is most commonly involved) in affected leg. If buttock or thigh claudication is present, the femoral pulse will be weak or absent indicating aortoiliac disease. At times pulsations are present at rest and disappear on exertion. (ii) Abdomen – to exclude aneurysm of abdominal aorta. (iii) Distal to obstruction limbs are cold to touch.

(c) *Auscultation* – of abdominal aorta, iliac arteries and femoral arteries down to the popliteal fossa may reveal stenosis by presence of a bruit.

Differential Diagnosis: See Table 113 for the differential diagnosis of intermittent claudication.

Investigations

1. *Ankle brachial pressure index* – Under normal conditions, systolic BP in the legs is slightly greater than that in the upper limb. The ankle brachial pressure index calculated from the ratio of ankle to brachial systolic pressure, is a sensitive index of arterial insufficiency. The highest pressure measured in any ankle artery is used as the numeratory of the index, a value > 1.0 is normal, and a value < 0.9 is abnormal.

   Measurement with Doppler probe

Table 113: Differential diagnosis of intermittent claudication

	Arterial claudication	*Neurological claudication*	*Venous claudication*	*Rheological claudication*
Site of pain	Calf usually	Along a dermatome	Calf always	Usually whole leg
Pain relief	Standing still	Lying down for 1/2 hour.	Leg elevation	Standing still
Signs	Absent distal pulses	Abnormal neurological signs after exercise	Signs of chronic venous insufficiency	Bounding pulses
Confirmatory tests	Ankle: brachial systolic ratio <0.8	MRI	Doppler of legs for DVT	Full blood count and ESR

A hand held pencil Doppler probe is placed over a patent pedal artery and the foot raised against a pole calibrated in mm Hg. The point at which the pedal signal disappears is taken as the ankle pressure.

2. *Exercise test* – is performed by exercising the patient for 5 minutes say on a tread mill. The ankle brachial pressure index is measured before and after exercise. A pressure drop (due to peripheral vasodilation) of 25% or more indicates significant arterial disease.
3. *ECG* – for evidence of ischaemia.
4. *Angiography* – to define extent of disease and possibility of bypass surgery or endarterectomy.
5. *Specialist diagnostic and therapeutic devices:* (a) Pressure wires with built-in pressure sensor at tip to measure translesional peripheral (and renal artery) gradients to determine hemodynamic importance. (b) Intravascular ultrasound for lesion assessment and for optimization after angioplasty or stenting. (c) Specific atherectomy devices to debulk, slice and remove plaque through long segments of heavily calcified lesions. (d) Excimer laser technology for endovascular ablation for total occlusions.

Management

Of chronic peripheral ischaemic disease.

A. ***Medical treatment*** – Indications: (a) If intermittent claudication is the only symptom and it does not interfere with the patient's employment. (b) Diabetes mellitus is not associated. (c) Presence of extensive disease contraindicates surgical interference. (d) Failure of surgery to relieve symptoms.

1. Measures to Prevent Progress of the Disease
   - Rest if presence of rest pain, wound or gangrene.
   - No smoking.
   - Reduction of obesity.
   - Care of feet – Skin should be protected from trauma, shoes should be comfortable. Avoid tight garters. Trim nails carefully. Avoid sitting with legs crossed. No operative removal of corns. If skin is dry, apply oil at night and dusting powder during day. Control of fungus infection.

     (a) Antiplatelet therapy – Aspirin 75–300 mg/day, if aspirin sensitivity, dipyridamole (200 mg bd) or clopidogrel (75 mg/day) or prasugrel (10 mg/day) or Ticagrelor 90 mg bd.

     (b) Cilostazol 100 mg bd one hr. before or two hrs. after breakfast and dinner if exercise alone is ineffective. It should not be used in patients of congestive cardiac failure.

     (c) Pentoxifylline, xanthine oxidase inhibitor, decreases blood viscosity and anti-proliferative action.

     (d) Control of lipaemia in atherosclerosis.

     (e) Adequate control of diabetes.

     (f) Control of thrombosing tendencies with long-term anticoagulants.

2. Measures to Increase Circulation

   (a) *Walking* – The patient should be instructed to walk slowly upto the point of claudication several times a day.

   (b) *Warm environment* – Hot bag to abdomen may cause vasodilation in lower limbs. Blood flow can often be stimulated by placing a thermostatically controlled heating unit over the lower extremities; the temperature within the box should not exceed 90°F. The source of heat is usually in the form of electric light bulbs. Heat must never be applied directly to ischaemic extremities.

   (c) *Active vascular exercise* – Buerger's exercise – Legs are elevated to 60° and kept in that position for 2–3 minutes until blanching occurs. Then dangle legs for 5 minutes till maximal flushing is seen. Then keep legs in horizontal position for 5 minutes. Contraindicated if infection or open wound.

   (d) *Passive vascular exercise* – (i) "Suction pressure treatment" – Alternate high and low pressure is produced in a hermetically sealed boot (Pavex boot). (ii) Saunder's oscillating bed for extremely old and debilitated patients in place of postural exercise. (iii) Intermittent venous occlusion – With a sphygmomanometer, the pressure is raised to about 60 mm Hg. For 2 minutes and released for 4 minutes, the process being repeated for half an hour.

   (e) *Other measures* – to alter flow properties of blood such as haemodilution, defibrination, plasma exchange and haemorheological drugs.

B. ***Interventional treatment***

(Revascularization) (See Table 114)

Procedures – (a) Percutaneous re-opening procedures– (i) Percutaneous transluminal angioplasty – is widely used for critical stenosis or occlusion. (ii) Local fibrinolytic therapy – as alternative or additional procedure to PTA, particularly if suggestion of recent thrombosis and it can be combined with thrombectomy. Streptokinase 6000 units/hr directly into the occlusion, with repeat arteriography after 6–12 hours. If significant improvement, treatment may be continued for 12–24 hours, with repeat arteriograms every 12 hours.

Table 114: Indications for revascularization

For	*Against*
Severe symptoms	Short history
Interference with everyday life	Continued smoking
Not better after exercise training	Severe angina or COPD
Stenosis or short occlusion	Long occlusion
Proximal disease	Distal disease
Unilateral disease	Multivessel disease

C. ***Reconstructive arterial surgery*** (limb salvage):
   - Indications – (a) Presence of severe claudication interfering with everyday work. (b) Critical leg ischaemia with rest pain or impaired skin and tissue viability and non-healing ulcers.
   - Procedure – Bypassing of occluded segment – Reconstructions above groin (aorto-iliac segment) give better results than those below the groin (femoro-popliteal segment). More distal bypasses to calf arteries only as alternative to major amputation.

Clues to renal artery stenosis

See Table 115.

Table 115: Clues to renal artery stenosis

- Known atherosclerosis
- Onset of hypertension before age of 30 or after age of 55 years
- Worsening of previously controlled hypertension
- Malignant or resistant hypertension
- Abdominal bruit
- Discrepancy of renal size
- Azotaemia not otherwise explained or worsened by ACEs or angiotensin II receptor blocker
- Recurrent congestive failure or flash pulmonary oedema in a hypertensive patient, particularly with preserved LV function.

Vasculopathy of specific aetiology - Non-atherosclerotic (VSE-NA) in young patient. PAD may be the first presentation of connective tissue disease (CTD) or thrombophilic state, younger age of onset, fever, wt. loss, multiple limb involvement, anaemia, high ESR, proteinuria and RBCs in urine all point to CTD, upper limb involvement being more common.

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

Inflammatory occlusive disorder involving small and medium-sized arteries and veins in distal upper and lower extremities, usually in males in age group 25–40. Heavy cigarette smoking is a predisposing factor. Increased incidence of HLAB^5 and A-9 antigens.

Clinical Features

1. ***Migratory superficial thrombophlebitis*** – Red painful areas on dorsum of foot particularly in region of ankle or lower leg and occasionally lower arm; often a vein 2 to 4 inches in length is involved. Slight malaise and little rise of temperature may be present. Lasts for 10 to 12 days and is followed by a brownish pigmentation.
2. ***Pain*** – One of the earliest symptoms, varies in intensity from mild to excruciating pain and often appears for the first time after exposure to cold. (a) Intermittent claudication occurs in almost all patients and is confined not only to calves but also occurs in feet. It is cramp-like and often occurs after progressively shorter intervals and lasts longer after cessation of activity. (b) Rest pain may be due to impending trophic disturbances. (c) Involvement of nerves causes sharp, shooting, lancinating pains in the whole extremity. Occasionally pain is relieved by keeping the leg down. Patient sits on edge of bed holding the involved foot, which is crossed over the healthy leg, in his hand.
3. ***Raynaud's phenomenon*** (RP) – Raynaud's phenomenon refers to reversible spasm of peripheral arterioles in response to cold or stress. RP is usually seen in distal digits but may involve nose, ears and tongue. It is characterised by triphasic response:
   - Phase 1: Pallor due to vasoconstriction of precapillary muscular arterioles.
   - Phase 2: Cyanosis due to venous pooling and deoxygenation of venous blood.
   - Phase 3: Erythema because of hyperaemia. It is associated with throbbing.

   Raynaud's phenomenon should be distinguished from Raynaud's disease which is occurrence of vasospasm primarily with no association with another illness (Primary Raynaud's). RP is secondary to other conditions, most commonly an autoimmune disease (Secondary Raynaud's) (Table 116).

Clinical Stages

1. *Premonitory stage* – Often unnoticed by the patient. Characterised by attacks of recurrent phlebitis, swelling of feet, loss of hair on the legs and formation of tender nodules in skin. The stage may last from 2 to 7 years.

Table 116: Differences between primary and secondary Raynaud's phenomenon

Primary RP	*Secondary RP*
• Exaggerated physiological response to cold or stress	• Secondary to underlying serious disease
• Symmetrical attacks	• Asymmetric intense painful attacks
• No tissue necrosis, ulceration or gangrene	• Ulcers and digital pitting present
• Median age of onset 14 yrs	• Age at onset >30 yrs
• No Cl. Fs. of CTD	• CTD, myalgia, fever, rash, wt loss, etc.
• ESR normal, CRP negative	• ESR raised, CRP positive
• Increased frequency of migraine and Prinzmetal angina may be present	• May not be present

Table 117: Causes of Raynaud's phenomenon

Primary or idiopathic (Raynaud's disease)
Secondary
• *Collagen vascular disease* – Scleroderma (usually benign form of CRST syndrome i.e. calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasis), SLE, RA, dermatomyositis, polymyositis.
• *Arterial occlusive disease.*
• *Neurological disorders* – Spinal cord tumors, syringomyelia, disc lesion, polio, carpal tunnel syndrome.
• *Exposure to cold*
• *Blood dyscrasia* – Cryoglobulinaemia, cold agglutinins, myeloproliferative disorders.
• *Trauma* – Prolonged use of vibrating tools, electric shock, cold injury, piano playing, typing.
• *Drugs* – β-blockers, ergot, methysergide, bleomycin, vinblastine.

2. *Stage of claudication* – Severe, cramping pains on walking which disappear after short rest and recur when the walk is resumed.
3. *Stage of rest pain* – Pain comes in paroxysms even at rest, is increased by elevation and relieved temporarily by lowering of the extremity.
4. *Stage of trophic changes and gangrene* – Pain constant and excruciating, vesicles on great toe followed by ulcers or fissures. Gangrene dry or moist spreading upwards.

Investigations

Arteriography – Smooth, tapering distal segmental vessels and fine network of collateral vessels.

Excision biopsy – of involved vessels confirms diagnosis.

Management

No specific treatment. Abstinence from tobacco. Arterial by-pass of larger vessels in selected cases and also debridement depending on symptoms and severity of ischaemia. Amputation if other measures fail.

RAYNAUD'S SYNDROME AND PHENOMENON

It is characterised by sequential development of white, numb 'dead fingers' (digital ischaemia), cyanosis, rubor of fingers (and toes) on exposure to cold, and subsequent flushing phase due to rewarming.

Classification: of Raynaud's phenomenon

Primary or Idiopathic (Raynaud's Disease)

No underlying cause. Occurs usually in females between 15 to 20 years of age. Family history common. Never progresses to ulceration (Table 117).

Management

(1) *Warm clothing* and avoidance of exposure to cold

(2) *Drugs* – (a) Adrenergic blocking agents. (b) Reserpine 0.25 mg to 0.5 mg orally od, or intra-arterial infusion of 0.5 mg into brachial or radial artery reduces pain and promotes ulcer healing. (c) Calcium antagonists Nifedipine or Diltiazem. (d) Prazosin.

(3) *Surgical sympathectomy* – if failure to respond to drugs, but effect transient.

Persistent digital ischaemia – Ischaemia of a digit or digits may last for days or weeks. Patients are usually middle age or elderly, often hypertensive. The cause is not obvious but may be due to occlusion of the digital artery by atheroma. At times polycythaemia vera or dysproteinaemia is the cause, or, in young subjects, a cervical rib may be responsible. *Treatment* – Spontaneous recovery is usual but for severe ischaemia reflex heating, analgesics and dextran infusion, and antibiotics for infection. Amputation along line of demarcation if gangrene occurs.

Cold injury – Freezing of tissues in hands and feet leading to frost bite can occur following prolonged exposure to cold. There is usually redness, blistering, infection and superficial gangrene of the digits of hands and feet. Treatment – Reflex heating, antibiotics and analgesics and dextran infusion. Deep tissues are usually preserved and skin gangrene separates out leaving a shrunken digit beneath.

Acrocyanosis – Reddish or bluish discolouration of hands and feet on exposure to cold occurring mostly in young women. It is thought to be due to arteriolar spasm with dilatation of venules in the skin. It may coexist with Raynaud's phenomenon. When the hand or foot is warm,

the skin becomes bright pink. Acrocyanosis may also be seen in elderly patients with cardiac disease and in neurological disorders such as stroke, poliomyelitis and multiple sclerosis. Treatment – Limbs must be kept warm. Sympathectomy may be necessary in patients with severe coldness and chilblains.

Livedo reticularis – occurs usually in young women. There is blotchy mottling and discolouration of feet and legs. It is likely to be due to patchy arteriolar vasospasm in the skin. A secondary form may occur in patients with polyarteritis nodosa or polycythaemia vera. It is as a rule localised to digits or feet and the condition may progress to gangrene.

PERIPHERAL VENOUS DISEASE VENOUS THROMBOSIS

Venous obstruction by thrombosis may be either a primary, simple, non-inflammatory process (*phlebothrombosis*), or a secondary reaction to local or distant inflammatory agents with active inflammation of the wall of the affected vein (*thrombophlebitis*).

Superficial thrombophlebitis particularly in case of migrating thrombophlebitis may involve normal veins without varicosis and is histologically characterised by chronic panphlebitis. This segmental, inflammatory phlebopathy is observed frequently in thrombophlebitis obliterans and, in carcinoma, and rarely in connective tissue disease and Behcet's syndrome.

DEEP VENOUS THROMBOSIS (DVT)

Table 118 lists predisposing factors for DVT.

Table 118: Predisposing factors for DVT

Predisposing factors
• **Patient factors**
– Elderly
– Prolonged bed rest
– Long air travel, prolonged sitting
– Obesity
– Varicose veins
– Oral contraceptives
– Pregnancy/puerperium
– Venous compression (tumour, aneurysm)
• **Medical conditions**
– Myocardial infarction
– Congestive heart failure
– Malignancy (pancreas, lung)
– Inflammatory bowel disease
– Nephrotic syndrome
– Behcet's disease
– Homocysteinaemia
• **Surgery**
– Hip fracture
– Abdominal or pelvic surgery
• **Blood disorders**
– Polycythaemia vera
– Thrombocythaemia
– Myelofibrosis
– Paroxysmal nocturnal haemoglobinuria
• **Deficiency of anticoagulants**
– Antithrombin III
– Proteins C and S
– Factor II or V Leiden
– Antiphospholipid antibody

Clinical Features

1. Pain usually in the calf, sometimes, also in ankle and joint. Feeling of tightness instead of pain.
2. Deep calf tenderness. Pain in calf on forced dorsiflexion of the foot (Homan's sign). Tenderness in femoral triangle.
3. Increased warmth in affected leg.
4. Fullness of superficial veins.
5. Increased local temperature.
6. Local oedema and induration.
7. Thrombosed vein may be palpable.
8. Slight cyanosis or discoloration.
9. Low grade pyrexia.
10. Sphygmomanometry cuff pain test – A BP cuff is tied round the involved part of the extremity and slowly inflated to 200 mm Hg and then deflated. Normally discomfort is experienced during inflation at above 160 mm Hg. In venous inflammatory disease, pain is experienced between 80 and 150 mm Hg.

Compression of the left common iliac vein by right common iliac artery is probably the reason why DVT is more common in the left than in the right leg.

Diagnosis

- *B-mode ultrasound* (compression ultrasound) or color-coded duplex ultrasound allows direct visualization of the thrombosis have an accuracy of 95%.

- *Plethysmography* is an indirect method which detects abnormalities in venous outflow caused by the thrombosis.
- *D-dimer test* - A negative test rules out DVT with high probability.
- *Phlebography* is mandatory before aggressive therapies such as surgical thrombectomy or fibrinolysis.

Management

A. ***Of established thrombosis***

1. General measures – (a) Complete bed rest until the process becomes quiescent. (b) Elevation of the extremities to diminish oedema. No active or passive movement of the limb. (c) Avoidance of coughing, straining at stool and deep breathing. (d) Dehydration should be avoided.
2. Specific drug therapy – (a) *Anticoagulants* – Heparin - 5,000 units initial bolus injection with continuous infusion or subcutaneous, followed by maintenance dose of 30,000-40,000 units/24 hours for 7 days or low molecular weight heparin once daily, combined with oral anticoagulants. Warfarin sodium is commenced at a dose of 10 mg/day after 7 days of IV heparin and then both drugs are administered together for at least 4–5 days. Warfarin should be continued for 3–6 months. Enoxaparin 1 mg/kg twice daily with normal renal function and Fondaparinux, an anti-Xa pentasaccharide, administered as a weight-based once-daily subcutaneous injection can be used instead of heparin and later switched to warfarin. (b) *Newer antocoagualnt* – Rivaroxaban, a factor Xa inhibitor, for treatment of acute DVT and acute PE as monothera py, without need of a parenteral anticoagulation overlap.
3. Surgical treatment – (a) *Thrombectomy* if free-floating thrombus in ileo-femoral segment, or in the rare patient with gangrene caused by venous thrombosis. (b) *Inferior venacaval interruption*– intraluminal (umbrella filter) or extraluminal useful in – (i) Patient with acute venous thromboembolism and absolute contraindication to anticoagulant therapy. (ii) Occasional patient with massive pulmonary embolism who survives, but in whom recurrent embolism may be disastrous. (iii) Very rare patient who suffers recurrent embolism while on adequate anticoagulant therapy.

B. ***Prevention of thrombosis in high-risk patients***

A significant reduction in thromboembolism in the high-risk group can be achieved by treatment aimed at altering the hypercoagulable state or preventing venous stasis:

1. Anticoagulants – low dose heparin 5,000 units subcutaneously 2 hours before operation, then every 8 hours for 7 days is effective in preventing pulmonary embolism. Oral anticoagulants also useful. Low molecular weight heparin 3500U s.c. 2 hr prior to surgery, followed by 2500U o.d. for 7 to 10 days.
2. Dextran – acts by coating venous endothelium and interfering with platelet stickiness and aggregation. Danger of overloading the circulation.
3. Drugs which inhibit platelet aggregation – Dipyridamole, aspirin, clopidogrel, prasugrel, ticagrelor.
4. Early ambulation – Post-operative and post-partum. Exercise of extremities while in bed.
5. Deep breathing exercises in bed.
6. Slight elevation of foot of bed for bed-fast patients.
7. Prevention of increased abdominal pressure by tight binders, etc.
8. Correction of cardiac failure.
9. Maintenance of adequate hydration.
10. Prophylactic femoral ligation – especially if repeated embolism.

III. **Obstruction of great veins**

1. **Superior vena caval syndrome:**

Causes – *Extravascular compression* – Bronchogenic carcinoma, mediastinal tumours such as Hodgkin's disease, leukaemias, benign tumours, aortic aneurysm.

Intravascular – Thrombosis, or rarely rupture of aortic aneurysm into SVC.

Symptoms – Fullness and flushing of face. Sometimes dyspnoea or dysphagia, occasionally convulsions.

Signs – Cyanosis and oedema of face, neck and arms. Dilated and tortuous superficial veins on thorax and upper abdomen. Prominent nonpulsating jugular veins. Inspiratory filling of neck veins and positive hepato-jugular reflux if obstruction is at or below entry of azygos vein into superior vena cava.

2. **Inferior vena caval syndrome:**

Causes

Extraluminal compression – Ascites, abdominal tumours, tuberculous plastic peritonitis.

Intraluminal – Carcinoma of kidney invading IVC, or thrombosis extending from pelvic veins.

Symptoms and signs – Cyanosis and oedema of legs with dilated varicose veins of legs and often abdominal wall. Dilated collateral veins on abdomen and chest with reversal of flow of blood in veins of lower abdominal wall (normally from above downwards). Ulcer due to stasis may develop on the leg in chronic cases.

CHAPTER 5

Haematology

1. LABORATORY DIAGNOSIS IN HAEMATOLOGY

BLOOD EXAMINATION

Complete Blood Count

A haematology analyser will measure directly:

Haemoglobin concentration.
Red cell count.
Mean (Red) cell volume (MCV).
Total white cell count (WBC).
Platelet count.

Other parameters derived by calculation are: Haematocrit (HCT) or packed cell volume (PCV). Mean corpuscular cell haemoglobin (MCH). Mean corpuscular haemoglobin concentration (MCHC). Normal blood counts vary with age and sex (Table 1).

Blood film: If any abnormality in FBC is detected a blood film must be examined.

Red cells: Appearance may suggest type of deficiency anaemia -

1. *Microcytic, hypochromic cells* in iron deficiency anaemia. Associated thrombocytosis if due to blood loss. If patient with microcytic anaemia does not respond to oral iron, possibility of β-thalassemia minor should be considered and estimation of HBA and HBA_2 levels carried out (Fig. 1).
2. *Macrocytosis* (MCV > 100 fl) suggests vitamin B_{12} or folic acid deficiency, while if MCV is in range of 100-110fl, it may be due to liver disease, alcohol abuse (without liver disease) or hypothyroidism, myeloma or myelodysplasia (Fig. 2).
3. *Dimorphic picture* (both small and large cells) – (i) Patients with iron deficiency responding to iron therapy. (ii) Mixed deficiency (both iron and folic acid). (iii) Sideroblastic anaemia. (iv) Post-transfusion. (v) Iron loss combined with hyposplenism – Coeliac disease, radical gastrectomy (incorporates splenectomy).

Table 1: Normal haematological values

Parameter		*Normal*
Haemoglobin (Hb)		13.5-17.5 g/dl
Red cell count	Males	4.6-6.5 x 10^{12}/litre
	Females	3.8-5.8 x 10^{12}/litre
Haematocrit (HCT)	Males	0.4-0.54
	Females	0.37-0.49
Mean corpuscular volume (MCV)		78-99 fl
Mean corpuscular haemoglobin (MCH)		27-32 pg
Mean corpuscular haemoglobin concentration (MCHC)		31-35 g/dl
RBC distribution width (A measure of variation in RBC size)		10.5-14.5
RBC mass		30 ± 5 ml/kg
Plasma volume		45 ± 5 ml/kg
Leucocytes		4.0-8.00 x 10^9/litre
Differential leucocyte count		
Neutrophils (40-75%)		1.5-7.5 x 10^9/litre
Lymphocytes (20-45%)		1.5-4.0 x 10^9/litre
Monocytes (2-10%)		0.2-0.8 x 10^9/litre
Eosinophils (1-6%)		0.04-0.4 x 10^9/litre
Basophils (< 1%)		< 0.1 x 10^9/litre
Platelets		150-400 x 10^9/litre
Serum iron		12-30 µmol/litre
Total iron binding capacity (TIBC)		45-70 µmol/litre
Serum ferritin	Males	24-314 µmol/litre
	Females	15-314 µmol/litre
Serum vitamin B_{12}		2.5-20 µg/litre
Serum folate		160-640 µg/litre
Red cell folate	Males	25-35 ml/kg
	Females	20-30 ml/kg
Plasma volume		40-50 ml/kg
Red cell half-life		25-33 days
Haemoglobin A_2		1.5-3.2% total Hb
Haemoglobin F		0.5-0.8% total Hb

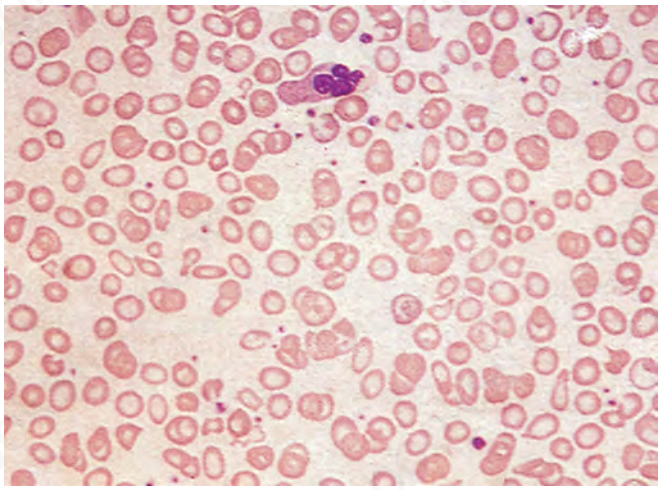


Fig. 1: Iron deficiency anemia (peripheral blood). Hypochromia, microcytosis, anisocytosis and target cells are shown

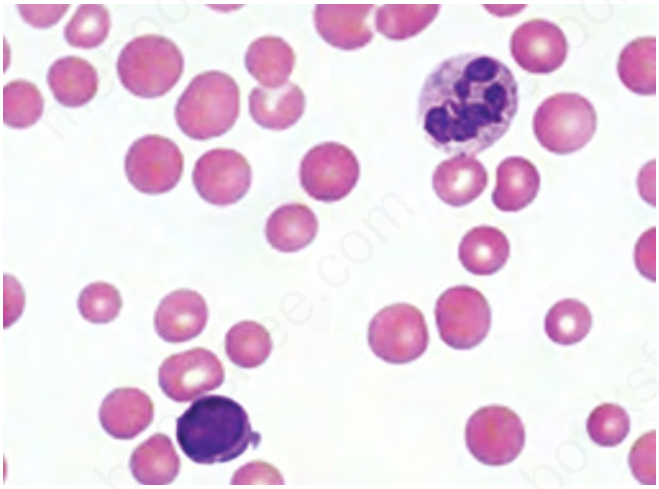


Fig. 2: Megaloblastic bone marrow. The majority of cells are megaloblastic erythroblasts showing failure of nuclear development and abnormal nuclear morphology of lymphocyte are visible and platelets are scattered through the film

4. *Polychromatic cells* (Young red cells larger than normal, greyish in appearance) suggests increase in proportion of reticulocytes, which may occur in response to bleeding or haemolysis, or during successful treatment of deficiency states.
5. *Red cell abnormalities* – common in haemolytic states – (a) *Sickle-shaped cells* in sickling disorders, the deformation resulting from partial solidification of the abnormal haemoglobin in hypoxic parts of the circulation (Fig. 3). (b) *Fragmented red cells* if damage to small blood vessels (microangiopathic haemolytic anaemia). (c) *Spherocytes* in hereditary spherocytosis (because of abnormal red cell membrane) and in autoimmune haemolytic anaemia (because small pieces of antibody-coated membrane have been removed by the spleen) (Fig. 4). (d) *Stomatocytes* are red cells which contains slit like area of central pallor and in a wet preparation they show a cup-shaped appearance. They are observed in hereditary spherocytosis, liver disease and Rh null phenotype. (e) *Target cells* – Red cells with central red area surrounded by a pale ring are found in (i) Liver disease. (ii) β-thalassemia minor. (iii) Some cases of iron deficiency (Fig. 5). (f) Tear drop cells – seen in myelofibrosis. (g) Echinocytes or burr cells – seen in uremia (Fig. 6). (h) Acanthocytes – seen in abetalipoproteinemia (Fig. 7).

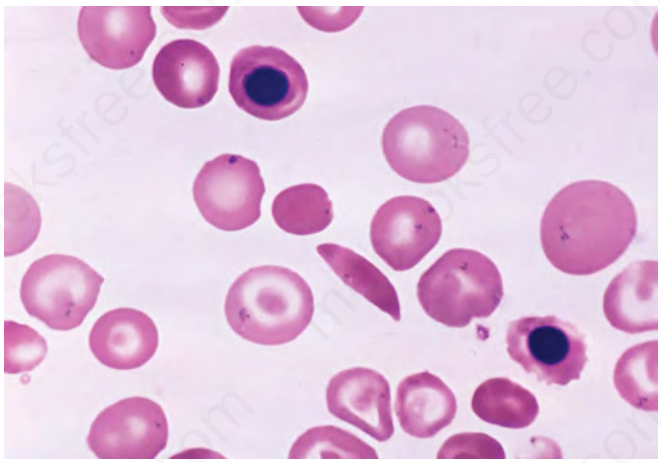


Fig. 3: Sickle hemoglobin disease (peripheral blood). In homozygous disease (HbSS), sickle cells and target cells are present together with occasional nucleated red cells. Heterozygotes (HbAS) have a normal peripheral blood

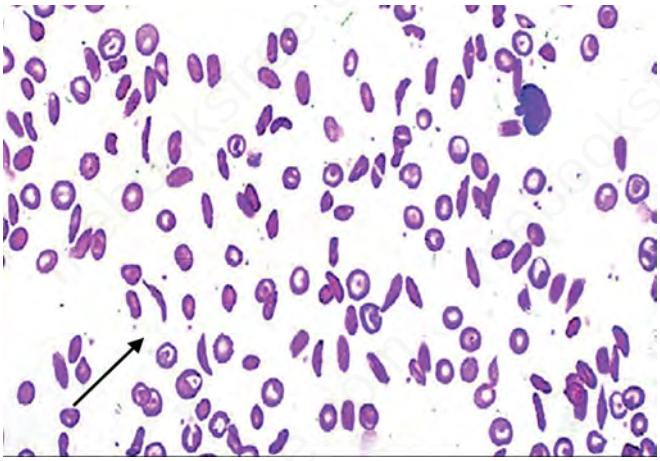


Fig. 4: Sickle cells—note the sickle shape due to the presence of HbS (arrow)

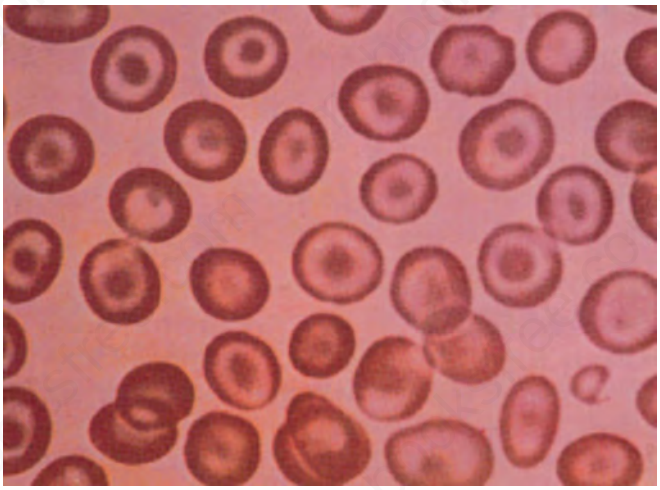


Fig. 5: Beta thalassaemia—plenty of target cells

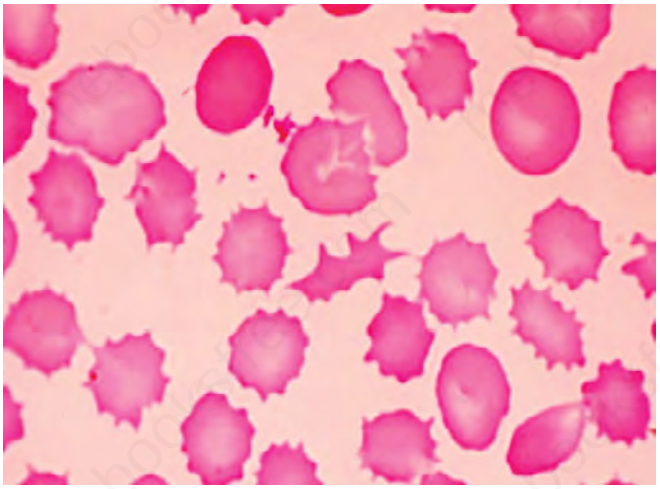


Fig. 6: Burr cells—note short spiny margins

Red Cell Indices

Mean corpuscular haemoglobin concentration MCHC denotes average concentration of Hb in red cells. Normal range 31-37 g/dl.

Mean corpuscular volume (MCV) indicates volume of red cells. Normal range 80-98 femto litres. If < 8 fl - 80 fl microcytes. If > 100 fl macrocytes. In certain dimorphic anaemias, MCV may be in normal range because of presence of both microcytes and macrocytes.

Mean corpuscular haemoglobin (MCH) indicates amount of Hb per red cell. Normal range 26-34 pg.

Higher CH in macrocytic anaemias. Lower MCH in microcytic hypochromic anaemias.

Inclusion Bodies in Red Cells

1. **Basophilic stippling**: Punctate basophils are granular inclusions blue black seen in megaloblastic anaemias, thalassemias, sideroblastic anaemias, lead poisoning, alcoholism and pyrimidine-5-nucletidase deficiency (Fig. 8).
2. **Pappenheimer bodies** are iron granules (aggregates of ferritin) in red cells due to incomplete Hb synthesis during erythropoiesis. They can be stained with Perl's stain. These red cells with Pappenheimer bodies are designated spherocytes and are seen in sideroblastic, megaloblastic and haemolytic anaemias and post-splenectomy.
3. **Howell-Jolly bodies** are nuclear remnants (aggregates of chromatin material), seen in RBCs, normoblasts. They are seen in megaloblastic anaemias (due to dyserythropoiesis, post splenectomy (due to loss of pitting function of the spleen) and in acute haemolytic anaemias (Fig. 9).

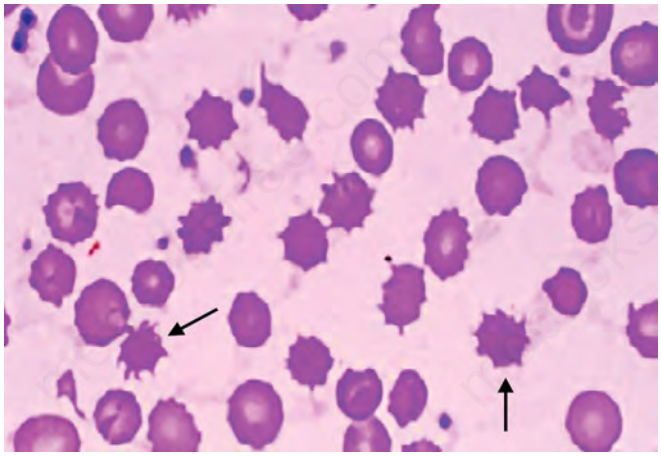


Fig. 7: Acanthocytes—note the thorn like projections

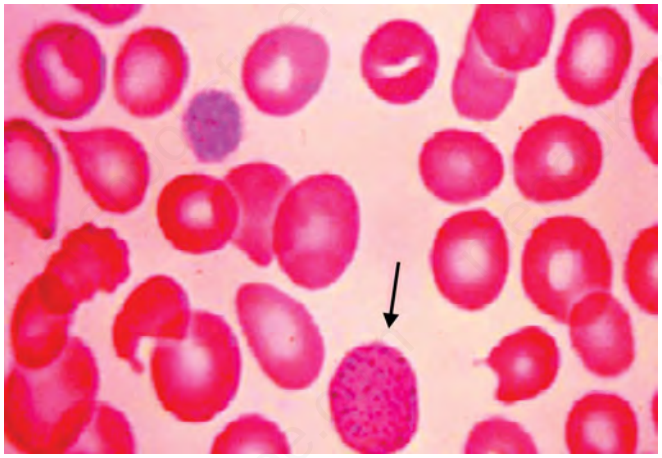


Fig. 8: Basophilic stipling—note the basophilic dots in the RBC, often due to toxic injury (arrow)

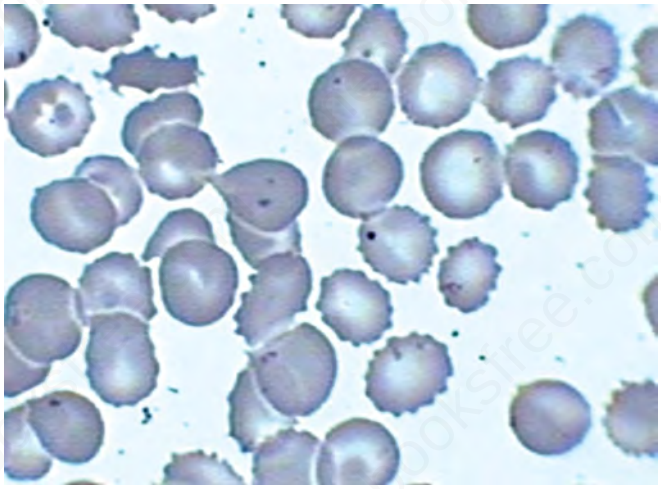


Fig. 9: Howell-Jolly body

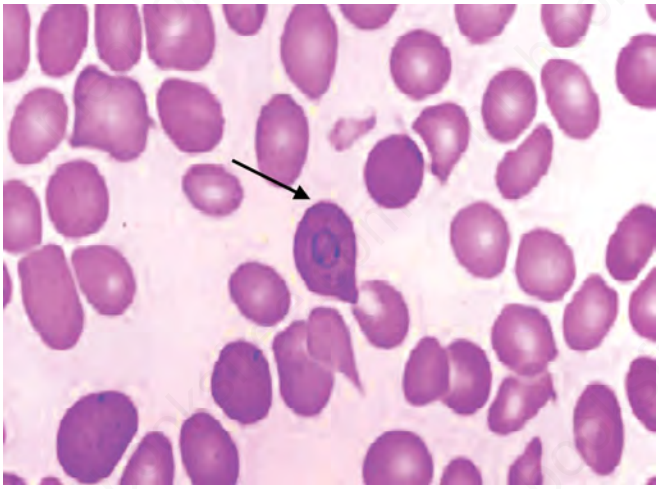


Fig. 10: Cabots ring which is remnant of nuclear material (arrow)

4. **Cabot's rings** are circular, oval or figure of eight shaped rings as a result of damage to lipoprotein of strauma of red cells. They are seen in megaloblastic anaemias (Fig. 10).
5. **Heinz bodies** are refractive and made up of denatured globin and are seen in G6PD deficiency, intake or exposure to oxidising drugs or chemicals and in unstable Hb disease.
6. **Haemoglobin H inclusions** are small and widely distributed β-chains in the red cells (golf-ball appearance) in α-thalassemias and in some cases of myelodysplastic syndrome (Fig. 11).
7. **HbC crystals** occur as a result of crystallization of HbC in some cases after splenectomy in homozygous haemoglobin C disease.

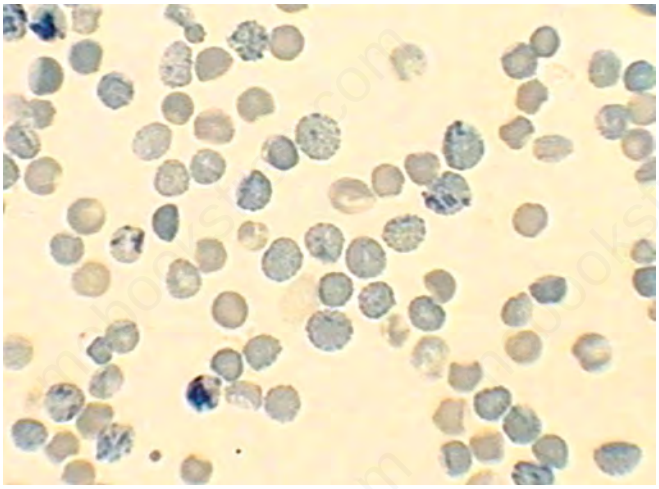


Fig. 11: HbH preparation showing golf-ball inclusions

White Cells

Neutrophil leucocytosis is seen during infection (particularly bacterial) and following tissue trauma or necrosis. A particularly marked neutrophilia may be termed a 'leukaemoid reaction' and may be seen in life-threatening infection, some cancers, and occasionally, in normal pregnancy. A marked neutrophilia is also characteristic of CML. *Neutropenia* – Occurs in (i) Infection – Viral, infectious mononucleosis. Tuberculosis, typhoid. (ii) Aplasia – Drug-induced: (a) Predictable (e.g. cytotoxic drugs). (b) Idiopathic. (iii) Marrow replacement – Leukaemia, lymphoma, myeloma, carcinoma. (iv) Megaloblastic anaemia. (v) Immune – SLE, Felty's syndrome.

Immature granulocytes released prematurely from the marrow in response to acute infection (Left-shift).

Leucoerythroblastic picture : Leucocyte precursors and red cell precursors (nucleated red cells) characteristic of bone marrow infiltration. 1. Myelofibrosis. 2. Marrow infiltration – Metastatic cancer (breast, prostate, small-cell lung), malignant lymphoma. 3. Osteopetrosis. 4. Metabolic–Gaucher's disease (usually with metastatic carcinoma).

Blast cells: In acute leukaemia development of leucocytes in marrow is arrested at immature stage, and in some cases this does not occur and blood picture is of neutropenia or pancytopenia (aleukaemic leukaemia).

Lymphocytosis: Often with many large reactive cells in viral infections, including infectious mononucleosis. In older patient it may suggest chronic lymphocytic leukaemia.

Platelets (Refer thrombocytopenia).

Other Blood Tests

Reticulocyte count: Reticulocytes are young (1-2 days old) red cells which still contain some residual nucleic acid material (demonstrated by a stain such as methylene blue) (Fig. 12). The count is typically raised in haemolytic states. Patients with chronic haemolysis are sensitive to events such as infection which may impair marrow compensation and the reticulocyte count may be used to anticipate a sudden fall in haemoglobin and need for transfusion.

Iron Status

Serum iron and *total iron binding capacity* (TIBC) are useful in diagnosis of microcytic and refractory anaemias – (a) In simple iron deficiency, serum iron low and TIBC raised. (b) Anaemia of chronic disease both iron and TIBC are depressed. In order to exclude coexisting iron deficiency, ferritin assay and marrow iron estimation may be necessary. (c) Raised serum iron and reduced TIBC – in conditions associated with increased iron accumulation, e.g. thalassemia, sideroblastic and dyshaemopoietic anaemias, haemochromatosis, transfusion siderosis (where the transferring iron binding sites are fully saturated).

Serum ferritin is a more accurate guide to iron status. It is low in iron deficiency. Raised in iron overload.

Serum vitamin B_{12} and folate assay should be done in patients with macrocytic anaemia, particularly if megaloblastic. Serum folate level can be increased by a recent meal.

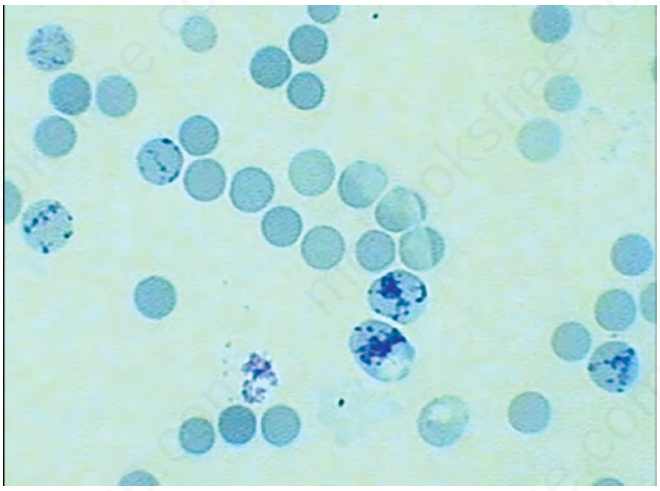


Fig. 12: Reticulocyte preparation of a patient with hemolytic anemia

Investigation of Haemolysis

Direct Coomb's test (antiglobulin test): Here an antibody directed against human immunoglobulin is used to detect the presence of antibody on the surface of the red cells by agglutination. The test is positive in nearly all cases of autoimmune haemolytic anaemia.

Indirect Coomb's test: Antibody in serum reacts with added 'O' cell suspension. On addition of antiglobulin, agglutination suggests positivity.

Gel card direct and indirect Coomb's test: Gel cards with incorporated anti-IgC + C and also anti-IG and anti-Ig can be separately used. Based on the same principle, it is a more sensitive method.

Haemoglobin electrophoresis: The haemoglobinopathies are the result of genetically determined amino acid substitutions within the haemoglobin molecule. Some of these mutations alter the net electrical charge of the molecule, so that the abnormal haemoglobin can be detected by electrophoresis – Sickle haemoglobin HbS as well as HbC, HbD and HbE. Carriers of β-thalassemia can be detected by elevated HbA_2 and this can detect mothers heterozygous for sickle-cell anaemia or β-thalassemia. This is particularly important for offering prenatal diagnosis.

Tests of Haemostasis

Coagulation tests – are performed on a blood sample anticoagulated with sodium citrate.

a. *Prothrombin time* – tests the extrinsic clotting pathway and is used to monitor oral anticoagulant therapy. Result is expressed as ratio compared with normal plasma.
b. *Partial thromboplastin (Cephalin-kaolin) time* – tests the intrinsic pathway. It is prolonged in haemophilia, patients on oral anticoagulants, heparin and in DIC.
c. *Thrombin time and fibrinogen titre* – assess conversion of fibrinogen to fibrin by thrombin. Thrombin time is commonly used to monitor heparin therapy and fibrinogen time to assess severity of DIC.
d. *Factor assays* – of individual clotting factors using adaptations of the above tests with known factor-deficient plasmas. Used for special investigation of bleeding disorders.

Normal Haematological Values

See Table 1 for normal haematological values.

Radioisotope studies – may be helpful in further investigation of haematological disease.

The following do not require imaging:

Red cell mass and plasma volume: Estimation of total volume of circulating red cells (red cell mass) is necessary for proper evaluation of polycythaemia. It is performed by labelling patient's own red cells with a suitable isotope $_{51}$Cr or 99m Tc, reinjecting a measured amount, and taking a blood sample after a suitable period of equilibration to enable the dilution to be calculated. In most cases plasma volume can be derived from red cell mass and peripheral blood haematocrit (except in presence of significant splenomegaly where it is inaccurate).

Red cell survival– can be measured by injected red cells labelled with $_{51}$Cr and counting the remaining radioactivity in blood samples taken at intervals afterwards. External counting over liver and spleen can give some idea of the rate of destruction of red cells at these sites. The test is time-consuming and seldom contributes much to evaluation of haemolysis.

Ferrokinetics: After IV injection iron is quickly cleared from circulation and used for erythropoiesis or stored as ferritin. The process can be measured following injection of radioactive iron salts and provides a clue into the mechanisms of various forms of anaemia, particularly those with ineffective erythropoiesis.

BONE MARROW EXAMINATION

The simplest form of marrow examination involves aspirating a small quantity of marrow from posterior iliac crest or sternum and making smears which are stained in similar manner to a blood film. Alternately histological sections can be made from aspirate marrow particles or from trephine biopsy sample.

Bone Marrow Aspiration

Indications: Investigation of:

1. ***Anaemias***:
   - *Megaloblastic anaemias*: Typical megaloblastic red-cells formation with presence of giant metamyelocytes. Similar picture also in pernicious anaemia, nutritional megaloblastic anaemia secondary to steatorrhoea, megaloblastic anaemia of pregnancy and that due to anticonvulsant drugs.
   - *Haemolytic anaemia* suggested by cellular normoblastic marrow.
   - *Aplastic anaemia*: Fat spaces predominate. Markedly reduced haemopoiesis.
   - *Sideroblastic anaemia*: Red cell precursors containing iron granules arranged in a ring round the nucleus (ring sideroblasts).
   - *Iron deficiency anaemia*: Assessment of marrow iron stores. In normal marrow 15% of red cell precursors show small iron granules within the cytoplasm.
   - *Unexplained and refractory anaemias.*
2. ***Cytopenias***
   - *Thrombocytopenia:* Differentiation of various thrombocytopenias depends on qualitative and quantitative assessment of marrow megakaryocytes.
   - *Neutropenias*: Marrow is normocellular and shows decreased mature neutrophils.
3. ***Haematological malignancy***
   - *Leukemias*: (i) Acute leukaemia – Infiltration with leukemic blast cells in the two common types ALL and AML are distinguished by morphological criteria and cytochemical stains. (ii) Chronic leukaemia – Aspiration allows examination of marrow cell morphology and examination for blast cells, which if above 15% may suggest impending blast transformation.
   - *Lymphoma*: For pre-therapy staging process. The extent of the disease at the time of diagnosis is the best guide to prognosis and treatment since bone marrow involvement invariably indicates advanced disease.
   - *Myeloproliferative disorders*: (i) Polycythemia vera – Particles aspirated are usually hypercellular; increased number of megakaryocytes are usually present and they are often large and multinucleate. (ii) Myelofibrosis – Bone marrow aspirate is usually dry. (iii) Essential thrombocythemia – Increase in number of megakaryocytes, which are often unusually large.
   - *Myeloma*: Marrow infiltration with plasma cells.
4. ***Carcinomatous infiltration***

   Leucoerythroblastic anaemia in which both normoblasts (immature red cells) and myelocytes (immature white cells) are present.

5. ***Infections and PUO***: (a) *Kala azar* –Amastigotes of L. donovani can be identified in stained material. (b) *Malaria:* Marrow tissue may reveal malarial parasites. (c) *Tuberculosis* – can occasionally be detected by culture. (d) PUO– Marrow examination is at times useful in difficult PUOs when one of these infections or malignancy is suspected.

Technique: The skin, subcutaneous tissue and periosteum over the posterior iliac crest (or manubrium sterni) are infiltrated with 2% lignocaine. The bone marrow aspiration needle is pushed through the bone with a boring motion, the guard being kept at a distance of about 1cm above the surface of the skin. When the needle has entered the marrow, the stillete is withdrawn and a long 10 ml syringe attached. Marrow aspirate is smeared onto glass slides. In selected patients, residual aspirate is placed in appropriate specimen containers for chromosomal analysis, microbiological culture, cell culture and electron microscopy and immune phenotyping.

M:E ratio – 500 marrow cells are counted, followed by calculation or percentage of different cells. Myeloid:Erythroid ratio gives the proportion of myeloid and erythroid cells. Normal M:E ratio is 3:1 to 15:1.

Assessment of iron stores on BMA:

0. No iron granules
1. Small granules in reticulum cells
2. Few small granules visible with low power lens
3. Many small granules in all marrow particles
4. Large granules in small clumps
5. Dense large clumps of granules
6. Very large deposits obscuring marrow cells

Table 2 lists causes of a 'dry' tap.

Bone Marrow Trephine Biopsy

Indications for bone marrow trephine biopsy are given in Table 3.

Technique: A Jamshidi-Swaim needle can be used to get the biopsy from the posterior iliac crest. After expulsion of 2 cm core of bone and its enclosed marrow from the needle, the biopsy specimen is smeared gently across three glass slides and then placed in fixative for subsequent histopathological processing and staining.

Iron stains: Prussian blue stains iron within erythroid cells and in marrow particles. In iron-deficient individuals, there is practically no stainable marrow iron, while the presence of ring sideroblasts is characteristic of sideroblastic anaemia.

Table 2: Causes of a 'dry' tap.

• Operator failure
• Primary myelofibrosis
• Hypercellularity (packed marrow, e.g. leukaemia)
• Lymphoma
• Carcinoma
• Hairy cell leukaemia
• Myeloid leukaemia plus myelofibrosis

Table 3: Indications for bone marrow trephine biopsy.

• To assess marrow cellularity
• Failure of marrow aspiration
• To detect focal involvement by malignant cells
• To demonstrate marrow fibrosis

Cytochemical stains– are occasionally used to help define the nature of an acute or chronic leukaemia. Lymphoblasts often give black positivity with PAS, whereas myeloblasts are Sudan-black positive, and monoblasts stain with nonspecific esterase and lysozyme. Neoblastic B cells of hairy cell leukaemia give a positive reaction with acid phosphatase.

Cell surface marker studies: The availability of monoclonal antibodies that recognise a wide variety of cell surface antigens has made it possible to identify cytological subgroups accurately, particularly those of white cell lineage. This has permitted a more accurate classification of the various forms of leukaemia, and is of therapeutic and prognostic significance.

Cytogenetic analysis: A wide variety of specific cytogenetic abnormalities are associated with subtypes of leukaemia, lymphoma and myelodysplasia, and these translocations have diagnostic and prognostic importance. Also the study of specific chromosomal changes is shedding light on the role of oncogenic activation in the genesis of neoplastic disease. For example, the Philadelphia chromosome translocation from chromosome 22 to chromosome 9 is pathognomonic of CML or Ph-positive ALL. Burkitt's lymphoma is another malignancy which is always associated with a translocation involving transposition of the *c-myc* oncogene from chromosome 8 to one of the immunoglobulin gene regions on chromosome 14, 2 or 22. These genes are then actively expressed by tumour B cells.

Clot section of the marrow: The clotted marrow is put in a vial with 10% formalin. Biopsy and sections are stained with haematoxylin and eosin. The results obtained are similar to those with a trephine biopsy.

Molecular biology techniques: It is possible to confirm the presence of clonal lymphoid proliferation by gene rearrangement studies: a B cell or T cell neoplasm will express a clonal pattern, whereas a reactive and hence non-neoplastic proliferation will not give rise to such a picture. These techniques have been further enhanced by the introduction of polymerase chain reaction (PCR), which can detect a tumour population of less than 1% cells.

2. HAEMATOPOIESIS

Haematopoiesis is the system of production of blood cells in response to the requirements of the body (Fig. 13).

REGULATION OF HAEMATOPOIESIS

1. Humoral - (a) Kidney secretes erythropoietin to stimulate erythropoiesis. (b) Thrombopoietin secreted by the liver stimulates platelet production.

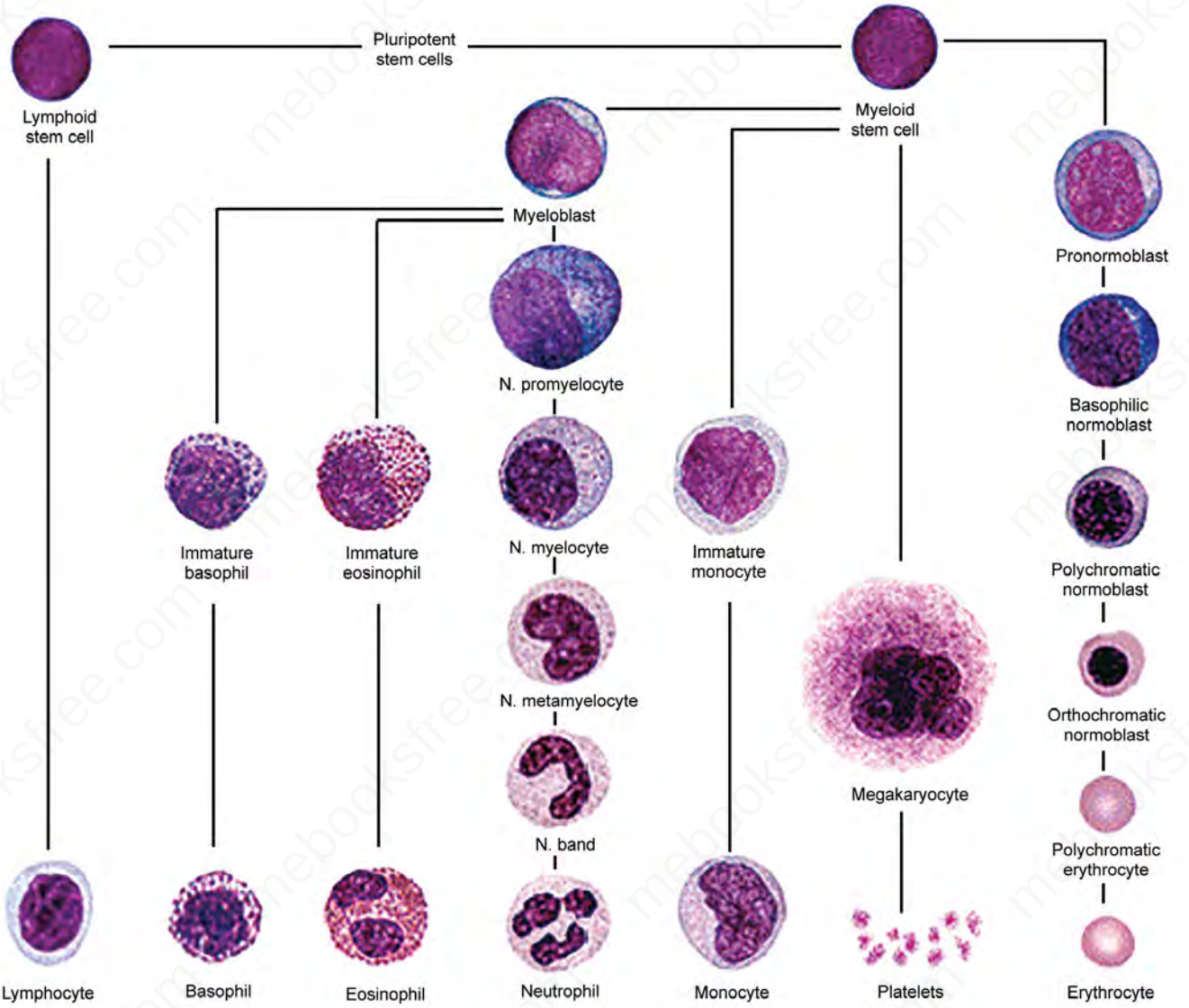


Fig. 13: Differentiation of haematopoietic cells

Table 4: Stem cell disorders.

• Chronic myeloid leukaemia
• Polycythemia vera
• Essential thrombocythemia
• Most acute leukaemias
• Aplastic anaemia
• Myelodysplastic syndrome
• Paroxysmal nocturnal haemoglobinuria

2. Inhibitory mechanisms - (a) Feedback mechanisms control over production of cells. (b) Roled apoptosis.
3. Cytokines produced by stromal cells.

TYPES OF CELLS

1. *Haemopoietic stem cells (HSC)* can proliferate to produce – (a) More stem cells. (b) Differentiate into progenitor cells. (c) Can produce different types of cells like RBCs, neutrophils, monocytes, platelets, lymphocytes, haemopoietic growth factors, etc. (d) A single haemopoietic stem cell can repopulate the whole marrow. Some of the stem cell disorders are listed in Table 4.
2. *Progenitor cells* – (a) are involved with one cell linkage – erythroid, myeloid, lymphoid or megakaryocytic. (b) These cells are formed from HSCs and are capable of proliferation and differentiation. (c) Early progenitor colonies may contain cells of more than one lineage, the late progenitor cells form cells of one lineage granulocytic or erythroid. These cells possess receptor for various cytokines and differentiate into maturing cells like proerythroblasts, normoblasts. Finally mature white cells, red cells and lymphocytes are produced.
3. *Maturing cells*

Haemopoietic growth factors (Cytokines) are hormone-like inducers of proliferation and differentiation of haemopoietic stem cells.

Functions of haemopoietic growth factors:

- Induce self-renewal of stem cells
- Proliferation and differentiation of progenitor cells
- Promotion of red cell and platelet production, amplification of leucocyte production

Types of haemopoietic growth factors:

- Granulocyte-Colony stimulating factor
- Granulocyte monocyte - Colony stimulating factor
- Erythropoietin

Table 5: Haematinics necessary for red cell formation.

• Amino acids for synthesis of chains of globin
• Iron for Hb synthesis
• Vitamin B_{12} and folic acid for nucleic acid synthesis of erythroid precursors
• Zinc
• Vitamin C to raise absorption of iron from ferric to ferrous state
• Vitamin E for maintenance of integrity of red cells
• Copper helps transfer of iron cells to plasma with aid of ceruloplasmin
• Thyroxine
• Androgen
• Cobalt trace element as part of vitamin B_{12}

- Thrombopoietin

Sites of haematopoiesis have three phases:

1. Mesoblastic period in the yolk sac during 3rd week
2. Hepatic phase from 6th to 30th week
3. Myeloid period: Haemopoiesis starts in bone marrow in the 4th month and at birth marrow is the principal site for haemopoiesis.

Erythropoiesis is the process by which progenitor cells in the marrow proliferate, differentiate into normoblasts and mature into anucleated reticulocytes which enter the circulation. The normal life span of RBCs is 110-120 days. Haematinics necessary for red cell formation are given in Table 5.

Process of erythropoiesis: Erythropoiesis is regulated by erythropoietin, vitamin B_{12}, folic acid and iron.

ERYTHROPOIETIN (EPO)

It is a glycolated protein derived mainly from kidney and small portion of liver. In the kidney by interstitial cells in vicinity of proximal convoluted tubules. These cells liberate EPO in response to anoxia (e.g. high altitude, lung diseases). Indications for use of Epo are listed in Table 6.

Action: EPO acts on erythroid precursors which possess EPO receptors and these proliferate in an attempt to correct anaemia.

Algorithm of Action of Erythropoietin on Erythroid Precursors is given in Figure 14

Myelopoiesis is the process which results in production of neutrophils, eosinophils, monocytes, macrophages and dendritic cells. Stages of myelopoiesis:

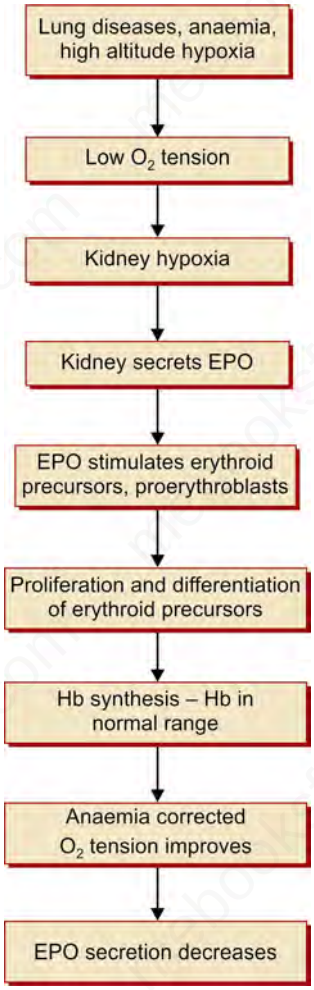


Fig. 14: Algorithm of action of erythropoietin on erythroid precursors

1. Haemopoietic stem cells – proliferate and differentiate into multipotent stem cells.
2. Multipotent stem cells (Progenitor cells) differentiate into colony forming units.
3. Colony forming units are the progenitors of granulocyte/monocyte pathway.

Red cell is a biconcave disc containing Hb and is bound by the red cell membrane. It has diameter of 7.2-7.7 microns (normocytic) with central one third pallor (normochromic)

ALTERATIONS IN SHAPE AND SIZE OF RED CELLS

1. *Macrocytosis*: Large RBCs with MCV > 100 fl, macrocytes in Folic acid and B_{12} deficiency are oval in shape (macroovalocytes)

Table 6: Indication for use of EPO.

• Chronic kidney failure
• Patients on dialysis
• Anaemia of chronic disorders
• Anaemia in malignancy
• Anaemia in HIV infection

2. *Microcytosis*: Smaller cells with MCV < 80 fl, microcytosis with increased central pallor (hypochromic) is seen in iron deficiency anaemia and thalassemia major and minor.
3. *Anisocytosis* suggests variation in red cell size. Mild variation is normal and not significant. It is observed in megaloblastic and haemolytic anaemias.
4. *Poikilocytosis* is variations in shape of red cell, e.g. tear drop cells, oval cells, helmet cells.
5. *Elliptocytosis*: Red cells elongated and oval in shape is seen in hereditary elliptocytosis and in macrocytic anaemias.
6. *Spherocytosis*: Spherocyte is a deeply staining cell where central pallor is not seen. Found in hereditary spherocytosis and autoimmune haemolytic anaemia.
7. *Target cells*: Because of redistribution of Hb, only periphery and central regions of the cells appear haemoglobinised. Observed in sickle cell anaemia, thalassemia major, haemoglobinopathies, post-splenectomy, hepatic disease.
8. *Sickle cells*: Thin, elongated, slightly curved RBCs in sickle cell disease.
9. *Schistocytes* (Fragmented cells): Irregular shaped, speculated and triangular helmet shaped are feature of microangiopathic haemolytic anaemia, DIC and cardiac haemolytic anaemia (Fig. 15).
10. *Stomatocytes* contain a slit like area of central pallor and are seen in hereditary spherocytosis, liver disease and Rh null phenotypes.
11. *Acanthocytosis*: Large irregular red cells with irregular spicules seen in alipoproteinemia, PK deficiency, vitamin E deficiency and liver diseases.
12. *Burr cells* with many red cell projections, regularly spaced and uniform in size. Seen in uraemia and drug-induced haemolytic anaemia in infants.

INCLUSION BODIES IN RED CELLS

- *Basophilic stippling* (Punctate basophilia). Fine to coarse blue black inclusions (altered ribosomes) seen in haemoglobinopathies, megaloblastic and sideroblastic anaemias, lead poisoning and alcoholism.

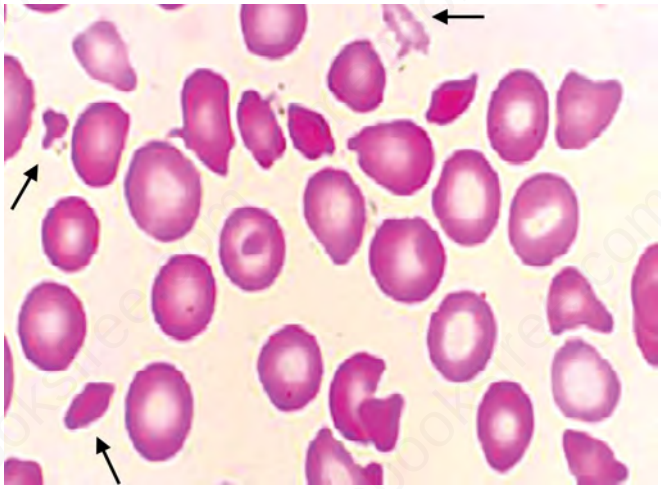


Fig. 15: Schistocyte—note the broken fragments of erythrocytes (arrows)

- *Pappenheimer bodies* are sclerotic granules, aggregates of ferritin located close to the cell membrane due to incomplete Hb synthesis. Such cells are called siderocytes and are found in sideroblastic, megaloblastic, haemolytic anaemias and postsplenectomy.
- *Heinz bodies* are refractive, seen close to red cell membrane and comprise of denatured globin. They are observed in G6PD deficiency, exposure to or intake of oxidizing drugs or chemicals, unstable haemoglobin disease.
- *Bite cells*: In acute haemolytic episodes, there is presence of microspherocytes and bite cells. As the spleen removes the Heinz body, a 'bite' is created in the red blood cell.
- *Cabot's rings*. Oval, circular or figure of 8 shaped artefacts as a result of damage to lipoprotein of stroma of red cells. Seen in megaloblastic anaemia.
- *Prickle cells*. Red cells having sharp, thorn-like projections in pyruvate kinase deficiency.
- *Howell-Jolly bodies* are remnants of nuclear material seen in red cells and normoblasts after extrusion of the nucleus. Observed in megaloblastic anaemias (because of dyserythropoiesis), postsplenectomy (lost pitting function of the spleen) and acute haemolytic anaemias.
- *Haemoglobin H inclusions* are free β-chains present in red cells of α-thalassemias and some cases of myelodysplastic syndrome. They are small and distributed throughout the red cell (golf ball appearance).
- *Haemoglobin C crystals*. Following splenectomy in haemoglobin C disease, there is crystallization of haemoglobin C, the crystals being tetragonal in shape.
- *Rouleaux formation*. Red cells become aligned in aggregates to resemble a stack of coins. This is seen in conditions in which there is increase of γ-globulin, e.g. multiple myeloma, Kala-azar, Waldenstrom macroglobulinemia and chronic inflammatory disease.

HAEMOGLOBIN

Haemoglobin made up of haem and globin is the main constituent of the red cell and imparts red colour to the erythrocytes.

Haem is synthesised (60–70%) in normoblasts while 30-35% is synthesised at the reticulocyte stage. Haem biosynthesis is regulated by the enzyme ALA synthase and Haem regulates the ALA synthase activity, suppressing it when haem is high, enhancing it when it is low.

Globin synthesis. In an adult each globin molecule is made up of 2 α and 2 β chains. Synthesis of these chains occurs in normoblasts. Globin synthesis is controlled by haem which stimulates it in reticulocytes.

Forms of Hb

- Haemoglobin A, A_2 present in adults
- Foetal Hb (HbF) - present from 8th week of foetal life to birth, when it contains 80% of HbF. It is elevated in β-thalassemic syndromes. Detection of HbF > 2% in a child/adult is suggestive of some abnormality of Hb synthesis.

3. ANAEMIAS

Anaemia is a state in which the haemoglobin concentration falls below the accepted normal range depending on age and sex.

CLASSIFICATION

I. Etiological

1. ***Blood loss*** – Acute or chronic post-haemorrhagic anaemia.
2. ***Impaired red cell formation***
   a. *Genetic disorders of haemoglobin synthesis* – Thalassemia syndromes.
   b. *Acquired deficiency of substances essential for haemopoiesis* – (i) Iron deficiency anaemia. (ii) Megaloblastic anaemia due to deficiency of vitamin B_{12}, folic acid, vitamin C. (iii) Protein malnutrition.
3. Haemolytic anaemias due to red cell destruction.
4. Defect in stem cell/erythroid precursor, (a) Aplastic anaemia (b) Pure red cell aplasia.

5. *Miscellaneous* - (a) Anaemia of chronic disorders- Infection/inflammatory disorders, kidney or hepatic failure. (b) Drug-induced disorders of erythropoiesis. (c) Infiltrative disorders of bone marrow – leukaemias, lymphoma, metastatic Ca, myelosclerosis.

II. According to Size of Red Cells and their Haemoglobin Content (Morphological)

- Microcytic, hypochromic (MCV < 78 fl)
- Normocytic, normochromic
- Microcytic (MCV > 100 fl)

PATHOGENESIS OF ANAEMIA

1. *Unbalanced cell growth*. Retarded DNA synthesis with normal RNA synthesis results in impaired cell division of erythroid precursors.
2. *Ineffective erythropoiesis* - Few red cells are formed because intramedullary death of intermediate and late megaloblasts.
3. *Haemolytic components* - Late normoblasts die in bone marrow because of a mild haemolytic process.

Investigation of a Case of Anaemia

I. History

Age and sex – Prematurity in infants. Females during reproductive period of life. G6PD deficiency confined to males. Sideroblastic anaemia mostly in males.

Rate of onset – Rapid onset over days, or one or two weeks suggests acute bleeding, acute leukaemia or haemolysis.

Drug ingestion – Especially aspirin and NSAIDs.

Occupation – Exposure to toxic chemicals.

Diet – History suggesting dietary deficiency.

Family history – of anaemia or jaundice common in congenital haemolytic anaemia. Occasionally in pernicious anaemia.

Bleeding – Blood loss commonest cause of anaemia – haematemesis, malena, bleeding piles, menorrhagia, haematuria, haemoptysis.

GI system – Symptoms suggestive of peptic ulcer, cirrhosis, neoplasm, hiatus hernia. Diarrhoea often intermittent and glossitis in megaloblastic anaemias.

Reproductive system – Menorrhagia. Number and interval between pregnancies.

Urinary system – Symptoms of kidney insufficiency such as nocturnal polyuria.

Nervous system – Paraesthesia in hands and feet in deficiency anaemias.

Bleeding tendency – as suggested by easy bruising or skin petechiae, prolonged bleeding after trivial injuries, or bleeding from more than one site.

Skeletal system – Bone pains may occur in anaemias due to marrow infiltration or replacement as in multiple myeloma, leukaemia, malignant lymphomas and myelosclerosis.

II. Physical Examination

Skin – Colour of skin, petechiae and ecchymoses. In pernicious anaemia the skin may have a lemon yellow tint, and in acute leukaemia an ashen tint. In hypothyroidism coarse and dry. Petechiae in anaemia suggest diagnosis of aplastic anaemia or leukaemia.

Nails – Brittleness and longitudinal ridging common in chronic iron deficiency anaemia, occasionally koilonychia.

Conjunctivae – show pallor due to anaemia. Icterus rare, when present suggests haemolytic anaemia or hepatic disease. Mild icterus may be seen in pernicious anaemia.

Mouth – (i) Mucous membrane – Petechiae on palate, cheeks, or tongue in aplastic anaemia and leukaemia. (ii) Gums – Hypertrophy in leukaemia especially monocytic. (iii) Tongue – Acute glossitis, or smooth tongue common in megaloblastic anaemia, occasionally in iron deficiency anaemia. (iv) Pharynx – Ulceration of throat may occur in acute leukaemia, and acute aplastic anaemia. (v) Angular cheilitis suggests iron deficiency.

CVS – Cardiac murmur in SBE. Haemic murmur may be heard in anaemia. Hypertension in anaemia due to kidney insufficiency.

Abdomen – 1. *Splenomegaly* – in leukaemia, haemolytic anaemias, megaloblastic anaemias, myelofibrosis, multiple myeloma. At times in severe iron deficiency anaemia. Splenomegaly is unusual in cases of aplastic anaemia, and secondary anaemia.2. *Abdominal lump* – e.g. in carcinoma of stomach, retroperitoneal mass of nodes in secondary carcinoma, chronic lymphatic leukaemia or malignant lymphoma. Localised tenderness may be present with peptic ulcer.

Lymph nodes – Superficial nodes may be palpable in leukaemia, malignant lymphomas and secondary carcinoma.

Bones – Bone tenderness especially sternal tenderness may occur in anaemias secondary to marrow infiltration,

e.g. in acute leukaemia, also in metastatic bone carcinoma, multiple myeloma, chronic leukaemia, myelosclerosis and malignant lymphomas.

Breasts – for evidence of carcinoma.

Rectal examination – for haemorrhoids or rectal bleeding. Size and shape of prostate gland.

Pelvic examination – in females with menorrhagia.

Fundus – Infiltration in leukaemia, retinitis in anaemia due to chronic kidney failure.

Severity of anaemia can be based on Hb levels:
Mild: Hb 9.1 -10.5 g/dl
Moderate: Hb 6-9 g/dl
Severe: Hb < 6 g/dl

Iron Distribution in Adult Male

Metabolism of iron – Iron is present in haemoglobin, myoglobin and iron containing enzymes of cytochrome system.

Haemoglobin – 2000-2500 mg

Myoglobin and enzymes: 400-500 mg

Iron stores – 500-1000 mg

Plasma iron – 2-3 mg

Storage of iron - (a) Haemosiderin - Brown pigment in reticuloendothelial cells of bone marrow. (b) Ferritin - It is present in circulation and reflects the iron stores and is used as a guide to control chelation therapy in thalassemia major.

Table 7: Causes of iron deficiency anemia.

1. *Increased physiological requirement*
   a. *Growth spurts* – Children between ages of 6 months and 2 years, and from 11 to 16 years due to spurts of growth during these periods.
   b. *Pregnancy*
2. *Pathological blood loss*
   - *Reproductive system*
     Menorrhagia
   - *GI tract*
     Bleeding
     Oesophagitis
     Oesophageal varices
     Hiatus hernia
     Peptic ulcer
     Malabsorption
     Coeliac disease
     Atrophic gastritis
     Inflammatory bowel disease
     Haemorrhoids
     Ca stomach, colorectal
     Hereditary haemorrhagic telangiectasia (rare)
   - *Dietary*
     Vegans
     Elderly
   - *Hookworm infection*

Changes in epithelia – Since the defect is in maturation, changes are manifested in all rapidly proliferating cells in bone marrow, oral mucosal stomatitis and chelosis cells, in epithelia of small intestine.

III. Investigations – (Refer)

MANAGEMENT

1. *Correction of dietary deficiency* – Faulty dietary habits, chronic alcoholism, malnourishment.
2. *Treatment of underlying cause* – Ankylostomiasis, piles, menorrhagia, infection, chronic kidney failure, leukaemia, liver disease, collagen disease or endocrine deficiency, surgical correction of intestinal abnormalities, e.g. blind loop.
3. *Removal of toxic chemical agent or drug* – in some cases of haemolytic anaemia or aplastic anaemia.
4. *Blood transfusion* – Chief value is its immediate effect.
5. *Administration of substances specifically lacking* – Principles are – (a) Haematinic should be started only after adequate blood examination, since response to a haematinic may obscure the blood picture. (b) The specific haematinic should be given alone. (c) The haematinic should be given in adequate doses for a sufficient period of time.

MICROCYTIC, HYPOCHROMIC ANAEMIA

The microcytic, hypochromic anaemias have a low MCV/MCH and involve a disturbance of iron metabolism caused by one of:

- Iron deficiency (lack of iron)
- Anaemia of chronic disease (impaired availability of iron)
- Thalassemia syndrome (defective globin chain synthesis)
- Sideroblastic anaemia (defective haem synthesis).

IRON-DEFICIENCY ANAEMIAS

Causes of iron deficiency anemia are listed in Table 7.

Clinical Features

A. ***Manifestation of underlying condition*** – e.g. pain of peptic ulcer, epigastric lump in carcinoma stomach.

B. ***Due to anaemia*** – Insidious onset of easy fatiguability, weakness, headache, bodyache, inability to concentrate, giddiness. With severe anaemia palpitation, exertional dyspnoea, anginal pain and congestive heart failure. Haemic murmur may be heard.

Table 8: Assessment of iron status.

Test	*Iron deficiency anaemia*	*Anaemia of a chronic disease*	*Sideroblastic anaemia*	*Thalassemia trait*
Serum iron	↓	↓	N	N/
Total iron-binding capacity	↑	↓	N	N
%Saturation	↓	N	N	N/
Ferritin	↓	N/	N	N/
Bone marrow iron stores	Absent	N/	+	N/
Sideroblasts	Absent	Absent	'Ring' sideroblasts	Present
Soluble transferrin receptor		N*	N	N*

C. ***Due to iron deficiency anaemia***

1. *Tongue* – Smooth and pale (bald tongue). Sometimes angular stomatitis.
2. *Dysphagia* (siderophagic) – most common in postmenopausal women, results from formation of mucosal webs at junction of pharynx and oesophagus (believed to be due to reduction in iron containing enzymes in epithelium and GI tract). The combination of splenomegaly, koilonychia and dysphagia is known as Plummer-Vinson or Kelly-Paterson syndrome.
3. *Dyspnoea and palpitation* especially on exertion. Angina pectoris and intermittent claudication may be observed.
4. *Atrophic gastritis* – associated with achlorhydria.
5. *Nail changes* – Nails may be thin and fragile. Platynychia and koilonychia. More frequent in adults.
6. *Hepatosplenomegaly* – usually mild degree may occur, regresses with correction of iron deficiency.
7. *Pica* – Perversion of appetite in form of geophagy or pagophagia (excessive eating of rice).
8. *Miscellaneous* – (a) Oedema of feet due to CHF, impaired kidney function or hypoproteinemia. (b) Amenorrhoea in females, sometimes menorrhagia. (c) Increased intracranial tension and papilloedema rare. (d) In children – Long-standing anaemia can cause fronto-parietal prominence and face resembling that in Cooley's anaemia. Also reduced attention span and poor learning. (e) Parotid gland swelling. (f) Hair loss. (g) Possibly impairment of T cell function and neutrophil killing thus promoting infection.

Investigations

1. Full blood count and blood film examination.
2. Haematinic assays (serum ferritin, Vitamin B_{12}, folate).
3. Urea and electrolytes.
4. Liver function tests.
5. Faecal occult blood.
6. Midstream urine (occult blood loss).
7. Fibreoptic and/or barium studies of GI tract.
8. Pelvic ultrasound (females, if indicated).

Diagnosis of iron deficiency anaemia:

1. Reduced Hb.
2. Reduced mean cell volume (< 76fl).
3. Reduced mean cell Hb.
4. Reduced mean cell Hb concentration.
5. Blood film: Microcytic, hypochromic red cells with pencil cells and target cells.
6. Reduced serum ferritin.
7. Reduced serum iron and total binding capacity.

Bone marrow stained for iron with Perls' stain confirms the diagnosis, presence of iron excludes iron deficiency.

Assessment of iron status in some anemias is given in Table 8.

Management

A. Eradication of the cause if possible

Treatment of ankylostomiasis, iron therapy from early stage of pregnancy, treatment of peptic ulcer, discontinuation of aspirin/NSAIDs, iron therapy for patients who have undergone gastric surgery. Correction of menstrual blood loss, and treatment of any other bleeding lesion.

B. Iron therapy

I. *Oral iron therapy*

1. *Calculation of daily dose:* In an average case of moderately severe anaemia, haemoglobin rises by about 1.0 g per cent per week of iron therapy. If we consider blood volume to be

4500 ml, total Hb. regenerated in a week comes to 45 g or in a day 6.4 g. Since each gram of Hb. contains 3.4 mg of iron, to produce 6.4 g of Hb iron required = 6.4 × 3.5 mg, i.e. about 22 mg. In moderately severe anaemia iron absorption would be about 20%, therefore oral dose of 100-120 mg. of elemental iron would suffice to provide adequate iron for optimum Hb rise.

2. *Preparations:* All ferrous salts (sulphate, gluconate, lactate, fumarate or succinate) are absorbed almost equally. Iron from ferric salts is poorly absorbed. Iron absorption is enhanced by combining iron salts with hydrochloric acid, ascorbic acid, succinic acid, fructose, cysteine, isonine and cobalt. Due to enhanced absorption, the dose of elemental iron can be reduced. This may be useful in the occasional patient who does not tolerate iron in the usual dose.
3. *Dosage and administration*: The optimum dose as stated earlier is 100-120 mg. of elemental iron per day. In order to avoid GI side-effects of therapy, it is advisable to start with a small dose (50 mg of elemental iron) and increase to full dose after few days. For sake of convenience preparations containing 30 mg or more of elemental iron per tablet or capsule are preferable so that patient can take one tablet b.d. or t.d.s. or as a single dose at bed time. Administration after food minimises gastric upset. Iron can be prescribed in the form of tablets, capsules, liquid or drops.
4. *Duration of therapy*: It takes about 8 weeks for Hb to reach normal level, irrespective of the initial Hb level. Replenishment of iron stores begins only after Hb level is normalised and this takes about 4 months. Hence iron therapy should be continued for 6 months.
5. *Side-effects*: Mainly gastrointestinal – Nausea, vomiting, epigastric pain, constipation or diarrhoea. Iron therapy may precipitate haemolysis in cases of paroxysmal nocturnal haemoglobinuria.

II. *Parenteral iron therapy*

1. *Indications*: (a) Intolerance of oral iron. (b) For getting rapid response – anaemia late in pregnancy, before surgery. (c) Continuous blood loss through GI tract due to inoperable conditions, e.g. intestinal polyposis or hereditary haemorrhagic telangiectasis. (d) Malabsorption. (e) GI conditions which may be aggravated by oral iron, e.g. peptic ulcer, ulcerative colitis, bleeding piles. (f) When patient cannot be relied upon to take oral iron.
2. *Preparation*

   Iron dextran (Imferon) – 100 mg IM by Z-track technique (Displacement of the skin laterally, before giving the injection), to avoid leakage of the drug into subcutaneous tissue with skin staining, or IV undiluted or diluted in form of drip for giving total requirement of iron at one sitting. A small test dose must be given IV before giving the total dose. Side effects – fever, joint pains, nausea, vomiting, diarrhoea, backache, bodyache, skin rashes, chest and abdominal pain, angio-oedema and fall of B.P. Anaphylactoid reaction may be fatal. Local or generalized lymphadenopathy may occur. (b) Iron-sorbitol – 100 mg by IM injection. Rapid absorption from injection site may cause saturation of iron-binding capacity, especially, if patient is on oral iron or has associated folic acid deficiency. Side effects – Flare up of urinary tract infection, fever, joint pains, nausea and vomiting.
3. Calculation of total dose – based on patient's body weight and haemoglobin level can be calculated from the formula: mg of iron (15 – Patient's Hb in gm/dl) × wt (kg) × 2.3 + 1000 mg. (Additional 1000 mg is for replenishment of iron stores).

Causes of refractory iron deficiency are listed in Table 9.

c. Blood transfusion: If rapid rise of Hb is required, e.g. (a) Worsening angina or severe co-existing pulmonary disease. (b) Iron deficiency with serious ongoing acute bleeding.

Table 9: Causes of refractory iron-deficiency.

1. Failure to take iron.
2. Continued bleeding.
3. Associated infection or malignancy.
4. Inefficient preparation prescribed, e.g. slow release preparations.
5. Wrong diagnosis – Thalassemia trait, sideroblastosis (congenital).
6. Predominant deficiency of B_{12} or folic acid.
7. Malabsorption of oral iron.

MEGALOBLASTIC ANAEMIAS

Megaloblastic anaemias are characterized by macrocytic blood picture (MCV > 100 fl) and megaloblastic bone marrow. Causes of megaloblastic anemia are enumerated in Table 10.

Clinical Features

1. *Due to anaemia:* Shortness of breath, dyspnoea, pallor and in older subjects angina or cardiac failure.
2. *Gastrointestinal:* Diarrhoea, loss of appetite and weight. Sore tongue due to glossitis and angular cheilosis. Mild jaundice (from intramedullary breakdown of haemoglobin and shortened red cell life span) may give the patient a lemon yellow tint.
3. *Neurological*
   a. Vitamin B_{12} neuropathy– due to symmetrical damage to peripheral nerves and posterior and lateral columns of sp. cord, the legs being more affected than arms. Psychiatric abnormalities and visual disturbances may occur (from folate deficiency).
   b. Neural tube defects– Folic acid supplements during pregnancy have been shown to reduce incidence of spina bifida, encephalocele and anencephaly in the foetus.
4. *CVS disease* – Raised serum homocysteine concentrations have been associated with arterial obstruction and venous thrombosis.
5. *Gonadal dysfunction* – Deficiency of either B_{12} or folic acid may cause sterility, which is reversible with appropriate vitamin supplements.
6. Knuckle pigmentation (Fig. 16).

Laboratory Diagnosis

1. ***Blood film*** (Fig. 17)
   - Macrocytosis – Hb content in red cells is proportionately increased hence normal MCHC.
   - Peripheral smear – (i) Oval macrocytes. (ii) Anisopoikilocytosis. (iii) Few tear drop cells and normocytes. (iv) Few nucleated RBCs. (v) Macrocytes without central pallor. (vi) Evidence of dyserythropoiesis – basophilic stippling, Cabot ring, Howell-Jolly bodies.
   - Haemoglobin decreased.
   - Hypersegmented neutrophils may be the first evidence of megaloblastic anaemia.
   - Iron ferritin level increases.

Table 10: Causes of megaloblastic anemia.

Vitamin B_{12} deficiency
1. Inadequate intake
• Strict vegetarians (vegans)
• Poor quality diet
• Elderly
2. Impaired absorption
Gastric
• Pernicious anaemia
• Congenital intrinsic factor deficiency
• Gastrectomy
Small intestinal disease
• Bacterial overgrowth (blind loop syn.)
• Crohn's disease and resection of terminal ileum
• Tropical sprue and non-tropical sprue
• Selective ileal malabsorption of B_{12}
• Fish tapeworm disease
• Coeliac disease (folic deficiency more common)
• Miscellaneous – HIV infection, severe pancreatic disease, drugs (e.g. colchicine, neomycin, metformin)
3. Increased requirement
• Pregnancy
• Disseminated cancer
Folic acid deficiency
1. Inadequate intake
• Malnutrition
• Old age
• Poverty
• Alcoholism
• Goat's milk
• Kwashiorkor
2. Impaired absorption
• Coeliac disease
• Dermatitis herpetiformis
• Tropical sprue
• Congenital folate malabsorption
• Oral contraceptives
3. Increased requirement
• Infancy, pregnancy
• Hyperplastic marrow due to haemolytic anaemia
4. Impaired utilization
• Folic acid antagonists
• Methotrexate
• Pyrimethamine
• Trimethoprim
• Anticonvulsant drugs
5. Increased loss (combined folic acid and vitamin B_{12} deficiency
• Tropical sprue
• Non-tropical sprue
• Haemodialysis

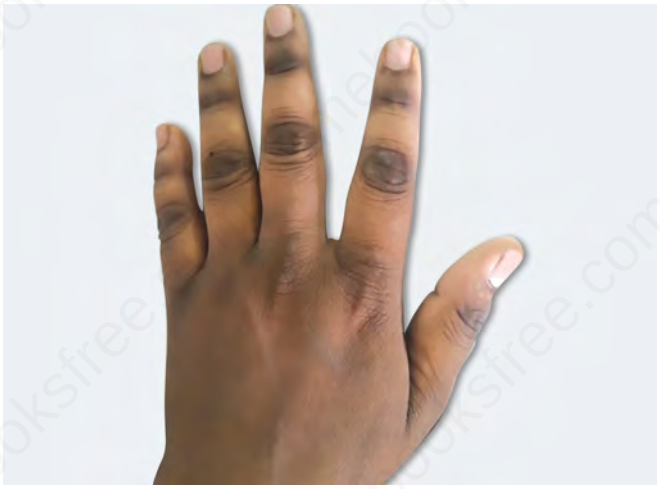


Fig. 16: Knuckle pigmentation

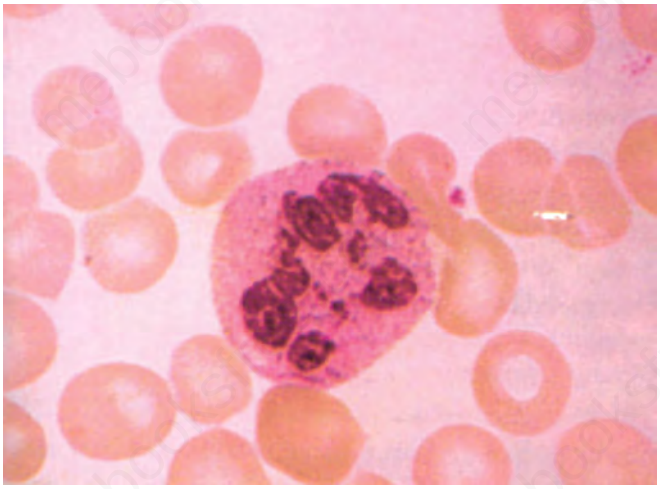


Fig. 17: Pernicious anaemia—macrocytosis with multilobed neutrophil

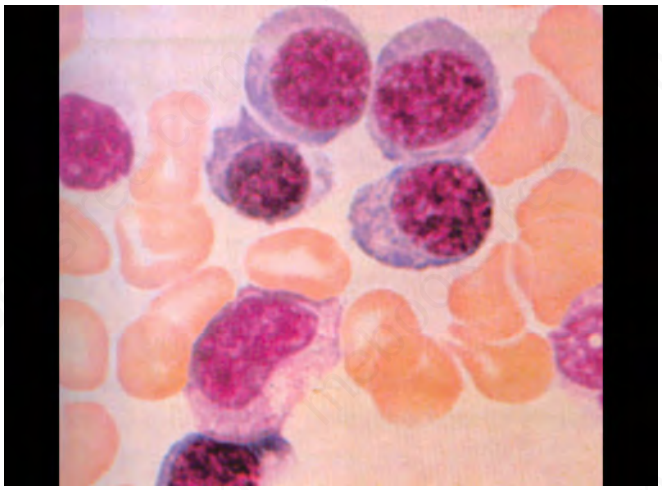


Fig. 18: Pernicious anaemia— megaloblasts in bone marrow

2. ***Bone marrow*** (Fig. 18)
   a. Hypercellularity with marked erythroid hyperplasia.
   b. Megaloblasts are larger than normoblasts and have sieve like nuclear chromatin. Evidence of dyserythropoiesis.
   c. Myelopoiesis – Giant metamyelocytes and giant band forms with abnormal nuclear shapes.
   d. Megakaryocytes with hyperlobulation and immature nucleus.
   e. Dimorphic anaemia – Macrocytes and hypochromic microcytes in cases of combined B_{12}/Folate and iron deficiency.

Changes in epithelia – With a defect in nuclear maturation changes are seen in all rapidly proliferating cells in oral mucosal cells, bone marrow, epithelial cells in small intestine.

3. ***Biochemical estimations***
   a. Serum folate levels – Decrease determined by isotope dilution method, microbiologic assay.
   b. Serum vitamin B_{12} levels – Decrease determined by isotope dilution technique or microbiological assay.
   c. Increased levels of methylmalonic acid in serum and urine in B_{12} deficiency.
   d. FIGLU excretion in urine in excess in folic acid deficiency.
   e. Deoxyuridine suppression test for deficiency of both vitamin B_{12} and folate.
   f. Schillings test of vitamin B_{12} absorption. Radioactive vitamin. B_{12} is used to assess intrinsic factor (IF) and Vitamin B_{12} to distinguish megaloblastic anaemia due to IF deficiency (pernicious anaemia) from other causes of B_{12} deficiency.
   g. Serum homocysteine levels – Increased in folate and B_{12} deficiency.

Diagnosis of Megaloblastic Anaemia

1. Oval macrocytes in peripheral smear.
2. Hypersegmented neutrophils.
3. Megaloblastic erythropoiesis in bone marrow.
4. Response to B_{12}/Folate therapy.

Causes of macrocytic anaemia with nonmegaloblastic (normoblastic) bone marrow are listed in Table 11.

Blood and bone marrow response to vitamin B_{12}/folic acid therapy: (a) Megaloblastic erythropoiesis returns to normoblastic erythropoiesis within 24 hours. (b) Reticulocytes increase from third day onwards. (c) Neurological symptoms – Increase in paraesthesias in first 6-7 days followed by progressive improvement.

Macrocytic anaemia in combination with other anaemias

1. B_{12} folate + iron deficiency anaemia – (a) Macrocytosis is masked. (b) Marrow reaction is macronormoblastic or megaloblastic and micronormoblastic.
2. B_{12}/Folate deficiency + thalassemia trait – Macrocytosis is masked.

Treatment

1. ***Vitamin B_{12} deficiency*** – (a) *Initial* –Hydroxycobalamin 1000 µg IM, 6 injections in 2-3 weeks. (b) *Maintenance* – 500-1000 mcg IM every3 months for life. In follow-up of patients with pernicious anaemia, a regular check must be kept for carcinoma of stomach. Iron deficiency due to atrophic gastritis, and hypothyroidism are important complications in patients on adequate maintenance. For patients sensitive to B_{12} injections or those who refuse injections, oral B_{12} (cyanocobalamin) in large daily doses (100 µg or more).
2. ***Folate deficiency*** – (a) *Initial* – Folic acid 5 mg. daily by mouth for at least 4 months. Folic acid in such big doses should not be given until B_{12} deficiency has been excluded, since folic acid may precipitate B_{12} neuropathy in a severely deficient B_{12} patient. (b) *Maintenance* – Need depends on whether the underlying cause can be reversed, e.g. gluten-free diet in coeliac disease.

Anaemia of chronic disease – is common in chronic infection, inflammation, connective tissue diseases and neoplasia and chronic liver disease. It may be idiopathic. The severity of the anaemia and morphological features depend on the duration of the underlying process. The anaemia is normocytic, normochromic initially, if the inflammatory process continues, it becomes microcytic and hypochromic. The microcystosis usually follows hypochromia. *Treat* underlying cause. Iron and folic acid. Transfusion of packed RBCs if indicated. Folic acid 5 mg daily. Pyridoxine 200-400 mg daily, discontinue if response after 3 months. Regular packed cell transfusions to maintain Hb. Elderly may require iron chelation therapy with desferrioxamine if serum ferritin level exceeds 2000 µg/litre.

Thalassemia trait: Thalassemia may be suspected when serum iron is normal or increased. MCV, MCH and RBC morphology are disproportionately abnormal relative to haemoglobin level, and RDW is normal. Haemoglobin studies including measurement of HbA_2 and HbF, and possibly examination for HbH bodies may be diagnostic. There should be no doubt about the diagnosis in a patient with raised serum iron and ferritin levels. NESTR of test: Family studies provide confirmation, but globin chain analysis or molecular technology may be required.

Table 11: Causes of macrocytic anaemia with non-megaloblastic (normoblastic) bone marrow.

• Alcoholism	• Reticulocytosis
• Liver disease	• Cytotoxic therapy
• Hyperthyroidism	• Chronic myeloproliferative disorder
• Aplastic anaemia	• Myelodysplastic syndromes

Sideroblastic anaemias – are a heterogenous group of refractory anaemias characterized by – (a) Presence of ring sideroblasts in bone marrow (Fig. 19). (b) Dimorphic blood picture – RBCs are microcytic hypochromic along with normocytic/macrocytic red blood cells. (c) Ineffective erythropoiesis. (d) Increased iron stores.

- *Aetiology* of sideroblastic anaemias – (1) Hereditary. (2) Acquired. (i) Idiopathic. (ii) Secondary to myelodysplastic syndromes, myeloproliferative disorders, leukaemias. (iii) Reversible type due to alcoholism, isoniazid, pyrazinamide, deficiency of copper or pyridoxine, lead poisoning.
- *Treatment* 1. Removal of cause where possible. 2. Vitamin. B_{12}, folic acid. 3. Iron depletion measures – (a) Chelating agents. Desferrioxamine 40 mg/kg/d infusion SC for 12 hours. 5 days in a week. (b) Phlebotomies, if anaemia is not severe.

PERNICIOUS ANAEMIA (PA)

Aetiology

(a) *Age* – 40-60. (b) *Sex* – more in females. (c) *Race* – incidence highest in North Europeans. (d) *Family history* – The disease is about 20 times more common in close relatives (sibs, parents and children). (e) *Cause* – It is an autoimmune disease in which antibodies to gastric parietal cells produce gastric atrophy and achlorhydria and antibodies to intrinsic factor interfere with its role in vitamin B_{12} absorption.

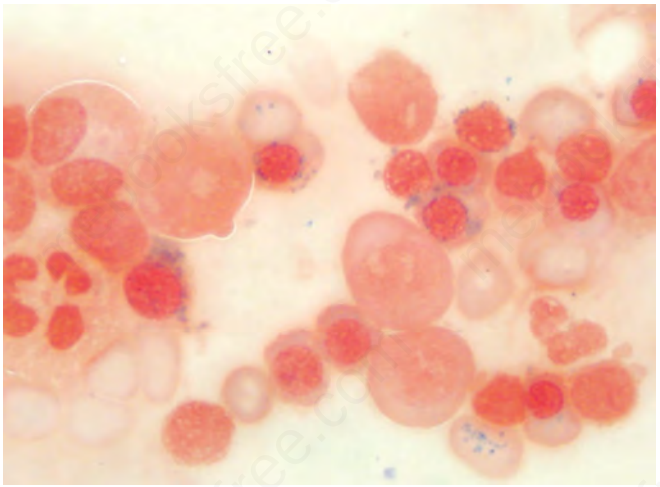


Fig. 19: Sideroblastic anemia

Cl. Fs. – Triad of weakness, sore throat and glove and stocking paraesthesia at presentation.

Associated Disorders

(a) In patient or in relatives – thyroid disease (Primary hypothyroidism, Hashimoto's disease or thyrotoxicosis), Addison's disease, hypoparathyroidism, immunoglobulin deficiency, and possibly with diabetes mellitus.(b) Correlation with early greying of hair, vitiligo, blue eyes and blood group A in patients or their close relatives. An association with human leukocyte antigen (HLA) 3. (c) Carcinoma stomach is three times more common.

Diagnosis

1. Laboratory studies – see macrocytic anaemia.
2. Endoscopy – to confirm atrophic gastritis and exclude gastric Ca or polyps which are 2-3 times more common.

Treatment – Injection of Hydroxycobalamin 50 μg every 4-8 weeks continued for life.

HAEMOLYTIC ANAEMIAS

A haemolytic anaemia is a reduction in the number of circulating red cells from their premature destruction.

Pathophysiology

When the normal lifespan (120 days) of red blood cell is shortened to such a degree that the bone marrow is incapable of maintaining a normal red cell mass leads to tissue anoxia. This results in increased output of erythropoietin stimulating production of red cells from the bone marrow. When the rate of destruction is in excess of eight times the normal, even a normal marrow cannot compensate and haemolytic anaemia results. Destruction of red cells can occur intravascularly, extravascularly or more commonly in both sites.

Classification of haemolytic anemias is given in Table 12.

Acanthocytosis of red cells and thrombosis, ophthalmoplegia and pigmentary retinopathy, may be involvement posterior columns and spinocerebellar tracts.

Recognition of Haemolytic State

1. **Evidence of increased RBC destruction**
   - Anaemia
   - Spherocytes, sickled cells, fragmented cells (damaged RBCs)
   - Increased urine urobilinogen
   - Increased serum unconjugated bilirubin
   - Decreased haptoglobin
   - Increased serum lactate dehydrogenase
   - Haemoglobinemia
   - Haemoglobinuria
   - Haemosiderinuria
   - Haptoglobin absent or markedly reduced
   - Reduced RBC survival
2. **Evidence of increased rate of red cell production** – Bone marrow expansion – Hypercellularity, especially of erythroid component may lead to skeletal deformity.
3. **Compensatory mechanisms**

Erythroid hyperplasia – Tissue hypoxia increases erythropoietin production, which in turn stimulates erythropoiesis, causing increase in number of marrow red cell precursors. With further stimulation, the volume of marrow increases, and when chronic haemolysis has been present from early childhood, there may be expansion of marrow cavities of the skull, vertebrae and long bones, causing marked skeletal deformities.

Stress cells and reticulocytosis – When erythropoiesis is under pressure, newly developed red cells are released from the marrow, causing large, deep-staining macrocytes ('stress' or 'skip cells') to appear in the blood and a variable reticulocytosis.

Effect of oxygen affinity – The degree of compensation in haemolytic process is modified by the oxygen affinity of the red cells. This is determined by the type of Hb and the level of intracellular phosphate. In pyruvate kinase deficiency, increased level of intracellular phosphate may explain how quite low levels of Hb are tolerated.

Failure of compensation – Anything which impairs the marrow's ability to compensate for haemolysis will lead to a fall in reticulocyte count and worsening of anaemia.

4. **Associated effects of a haemolytic state**

   (a) Depletion of folate stores. (b) Viral infection particularly with human parvovirus B_{19}, causes a transient failure of erythropoiesis and dramatic fall in Hb level in a patient with haemolytic anaemia. (c) Work hypertrophy of the spleen.

Table 13 lists important laboratory findings in haemolytic anaemias.

Clinical Manifestations

1. Pallor – severity as per degree of anaemia
2. Hyperdynamic circulation
3. Icterus – mild to moderate
4. Splenomegaly
5. Gall stones.

Table 12: Classification of haemolytic anemias.

Intrinsic RBC abnormality (inherited)
Membrane defect
• Hereditary spherocytosis
• Hereditary elliptocytosis
• Stomatocytosis, Acanthocytosis
Metabolic defect
• Shunt pathway – G6PD deficiency
• Embden - Meyerhof pathway – Pyruvate kinase deficiency
Haemoglobin defect
• HbD, HbE and other haemoglobinopathies
• Thalassemias
Extrinsic RBC abnormality (acquired)
Antibody - mediated
• Haemolytic blood transfusion reaction – ABO
Haemolytic disease of the newborn
• Autoimmune haemolysis
Warm or cold antibody
Drug-induced
Nonantibody mediated
• RBC fragmentation
Prosthetic heart valve
Thrombotic thrombocytopenic purpura
Haemolytic uremic syndrome
Pre-eclamptic toxaemia
Disseminated intravascular coagulation
Meningococcal septicaemia
Paroxysmal nocturnal haemoglobinuria
• Infections
Plasmodium falciparum malaria
Clostridium welchii
Mycoplasma pneumoniae
Infectious mononucleosis
• Chemicals and drugs
Oxidant drugs
Dapsone, salazopyrine
Arsine, primaquine
Nitrites
Burns
Fresh water drowning
• Paroxysmal nocturnal
haemoglobinuria
(acquired membrane defect)
• March haemoglobinuria
• Severe vitamin E deficiency

Test for Diagnosis of Haemolytic Anaemia

Basic tests

- Direct antiglobulin test – for investigating any suspected immunological disorder (particularly warm-type)

Table 13: Laboratory findings in haemolytic anaemias.

• S. bilirubin (unconjugated)	Raised
• Urine urobilinogen	Raised
• Rate of bilirubin production	Raised
• Red cell life span	Decreased
• Haptoglobin	Decreased (++)
• Serum LDH	Raised

- Haemoglobin electrophoresis, sickle test, HbA_2 and HbF levels, H-body preparation, testing of haemoglobin instability, globin chain analysis
- Compliment fixation test for PNH
- Glucose-6-phosphate dehydrogenase screen assay, pyruvate kinase assay
- Osmotic fragility and autohaemolysis for hereditary spherocytosis/elliptocytosis, RBC membrane analysis
- Serum LDH levels increased

Specific test

Chromium - 51 - labelled RBCs

Can be tracked for survival and site of destruction

Treatment

Patients with compensated haemolytic process require no treatment. Otherwise, management is general and specific. Folic acid 5 mg is given routinely, and lifelong in those with inherited haemolytic disorders.

I. CONGENITAL HAEMOLYTIC ANAEMIAS

A. **Red cell enzyme deficiencies**

1. ***G6PD deficiency*** – G6PD protects red cells against oxidant damage, e.g. from certain drugs (mainly sulphonamide and antimalarials chloroquine and primaquine). G6PD deficiency is an X-chromosome linked trait. *Clinical features* – (a) Drug-induced haemolytic anaemia. Ingestion of the drug is followed by fever, malaise, prostration, passage of dark urine, and acute anaemia. (b) Favism. (c) Neonatal jaundice. (d) Congenital non-spherocytic haemolytic anaemia. Haemolysis during intercurrent acute illness. *Diagnosis* – established by enzymatic assay.

It is seen in region endemic for Plasmodium falciparum, as it is known to confer resistance against this infection.

Treatment: Avoidance of drugs (Table 14), fava beans. In case of hemolysis develop no specific treatment unless severe, in those cases blood transfusion considered. If acute renal failure develops, hemodialysis may be needed.

G6PD variants

Class I Hereditary	Nonspherocytic haemolytic anaemia
Class II	Severe deficiency
Class III	Mild to moderate deficiency
Class IV	Non deficient variant

2. *Pyruvate kinase (PK) deficiency* – usually presents early in life with haemolytic anaemia, jaundice and splenomegaly or sometimes with neonatal jaundice. Because of PK deficiency synthesis of ATP is impaired and thus life span of RBCs is reduced. Diagnosis can be confirmed by PK assay of red cells. *Treatment* – As there is increased turnover of cells, oral folic acid supplementation is given. Splenectomy is useful in severe cases. Prenatal screening advised to mother who had child with pyuruvate kinase deficiency.

B. **Haemoglobinopathies**

Haemoglobinopathies are inherited disorders of haemoglobin structure or its production. Human haemoglobin is a globular protein and consists of a protein part (globin), combined with four haem groups.

Classification

1. *Structural haemoglobinopathies* – A structural abnormality of one of the globin chains, usually caused by a single amino acid substitution.
2. *Thalassemias* – which are caused by an inherited defect in the rate of synthesis of one or more of the globin chains. This results in underproduction of haemoglobin, and imbalanced globin chain synthesis – with precipitation of the chains produced in excess, and the formation of rigid inclusions (Heinz bodies).

A. SICKLE CELL DISORDERS

Genetic Sickle Cell Disorders

Sick cell disorders are characterized by presence of HbS-sickle haemoglobin which give sickle shape to RBCs in a state of reduced oxygen tension.

1. ***Sickle cell trait*** – Less than 50% HbS per cell is usually not associated with clinical abnormality. Infarction of spleen may occur during anaesthesia, and hematuria is not uncommon.
2. ***Sickle-cell anaemia*** – Anaemia from about third month of life, since HbS is more than 70% in red cells.
3. ***Sickle cell disease*** – This refers to all disease states in which at least one gene is of HbS.

Table 14: Drugs and chemicals that should be avoided by persons with G6PD deficiency.

Sulpha drugs
• Sulphanilamide
• Sulphapyridine
• Salazopyrine
• Septran
• Dapsone
Antimalarials
• Primaquine
Analgesics
• Aspirin
• Acetanilid
• Phenacetin
Nitrofurans
• Nitrofurantoin
• Nalidixic acid
• Furazolidine
Miscellaneous
• Vitamin K analogues
• Naphthalene
• Toluidine blue
• TNT
• Probenecid
• Dimercaprol

Pathogenesis: Clinical problems in sickle cell disease relate to veno-occlusion caused by polymerization of deoxygenated haemoglobin S. This results in the pathognomonic change in the shape of erythrocytes to the sickle shape that stiffen the RBC membrane, increase viscosity and cause dehydration due to potassium leakage and calcium influx. The most common clinical feature is the painful vaso-occlusive crisis resulting from blockage of small vessels. However, large vessels disease also occurs, resulting in – Thrombotic cerebrovascular accidents, acute sickle chest syndrome, and placental infarction.

Clinical Features

1. ***Delayed growth and development***
2. ***Enlargement of spleen*** after 6 months. Later at 5-6 yrs of age, reduction in size due to multiple infarcts from veno-occlusion of branches of splenic artery. In adults, spleen may be totally replaced by fibrous tissue (autosplenectomy).

3. ***Leg ulcers*** – Shallow ulcers near ankle due vascular stasis and often after trauma.
4. ***Hand-foot syndrome*** – Painful swelling of hands and feet. Vaso-occlusive crisis and dactylitis leads to destruction of metacarpals, metatarsals and phalanges.
5. ***CNS*** – Brain syndrome in a few children, occlusion of cerebral vessels leads to stroke.
6. ***Infections*** – Pneumococcal pneumonia, meningitis due to hyposplenism, osteomyelitis due to salmonella from repeated bone infarcts.
7. ***Cardiomegaly*** due to hyperdynamic circulation as a result of chronic anaemia.
8. ***Hepatomegaly***
9. ***Gall stones*** – Pigment gall stones increase in frequency from childhood to adult.
10. ***Ocular complications*** – Occlusion of retinal vessels causes retinal changes such as 'salmon patches', intraretinal haemorrhages, A-V anastomosis.
11. ***Abdominal pain*** occurs due to infarcts of abdominal viscera due to vaso-occlusive crises.
12. ***Priapism*** – due to stagnation of blood in corpora cavernosa.
13. ***Skeletal changes*** – In a young child there is widening of the diploe of the skull leading to new bone formation with resultant 'crew cut appearance' in X-ray. Bone and joint ischemia leading to aseptic necrosis seen in femoral and humeral head. Unusually susceptibility to osteomyelitis, caused by salmonella.

Complications of Crises in Sickling Syndromes

Sickling and periodic exacerbations (crises) when patient is exposed to extreme hypoxia vaso-occlusive syndromes.

- *Painful crises* are usually the result of either reduced blood flow leading to tissue infarction, or sequestration of sickled RBCs in various organs. Crises can be precipitated by infection, dehydration and exposure to low temperatures. In first year of life, a common presenting feature is painful swelling of hands and feet 'hand-foot syndrome'. In older children and adults, severe pain in the limbs and back associated with fever and prostration. Less commonly sickling may give rise to cerebral or pulmonary infarction.
- *Aplastic crises* are characterized by falling Hb level, and absent reticulocytes and are caused by parvovirus B_{19} infection.
- *Haemolytic crises* – Marked increase in haemolysis.
- *Sequestration crises* occur when sickled RBCs pool in spleen, liver or lungs. Splenic enlargement is a life-threatening complication seen in early childhood. It is characterized by massive enlargement of the spleen, together with sharply falling Hb level and rising reticulocyte count. A serious chest syndrome can occur, with bilateral radiographic changes, tachycardia, fever, profound hypoxemia and rapidly falling Hb level. The steady state Hb level is 5-11 g/dl. Blood film shows polychromasia, target cells and irreversibly sickled RBCs.

Sickle cell Hb C (SC) disease tends to have a milder clinical course than sickle cell anaemia. However in addition to complications seen in sickle cell disease, there is a higher risk of proliferative retinopathy due to retinal veno-occlusion.

Haematology in Sickle Cell Anaemia

- Anaemia – moderately severe
- WBC – slightly elevated
- Platelets – elevated
- Peripheral smear – Anisopoikilocytosis

There are sickle cells, target cells and ovalocytosis. Also polychromatophilia with few stippled RBCs.

Diagnostic Tests

1. *Sickling test* – Sickling is induced by adding reducing agent like 2% sodium metabisulphite to blood.
2. *Hb electrophoresis* can be performed on cellulose acetate membrane or starch agarose. HbS is a slow moving Hb as compared to HbA and HbF.
   In HbS, HbS constitutes 70-90% of total Hb but HbA is nil. This differentiates homozygous (SS) from heterozygous state (SA), since the latter demonstrates two bands of HbS and HbA.
3. *HbF estimation* since HbF is 10-30% in homozygous state and is helpful in assessing course of the disease.
4. *High performance liquid chromatography* (HPLC) gives exact amount of HbA, HbS, HbF and HbA_2.
5. *Globin chain analysis* may be required to assess the genetic basis of disease and differentiate it from various heterozygote states.
6. *HbS solubility* is based on the fact that sickle Hb is insoluble in deoxygenated state.

Management

a. Between crises – Patient should be given folic acid regularly, and infection treated early with antibiotics. Hydroxyurea helps by – (i) Reducing incidence of sickling crises. (ii) Increase in HbF levels in RBCs which can carry more O_2 and reduce tissue hypoxia. (iii) Lowering of blood viscosity thereby reducing occurrence of veno-occlusive crises.

b. During crises – Rest, analgesics, hydration, correction of acidosis, plasma volume expander and oxygen.

c. Blood transfusions – if PCV falls dangerously, cerebrovascular symptoms in early childhood, recurrent pulmonary thrombotic episodes, and to suppress the sickling process, e.g. to permit major surgery, during pregnancy or to 'break' a cycle of painful crises.

d. Further management – Bone marrow transplantation offers opportunity for cure. Criteria for acceptance – (i) Sibling matched for HLA. If sibling match not present, to consider a matched, unrelated donor. (ii) Presence of one or more of – Neurological deficit, CVA or SAH. (iii) Two or more episodes of acute sickle chest syndrome or stage I and II chronic sickle lung disease. (iv) Recurrent severe and debilitating pain. (v) Problems for future medical care.

e. Gene therapy is under investigation.

B. THALASSEMIAS

Thalassemias are genetic disorders of Hb synthesis in which there is reduced production of one or more chains of Hb. This results in a relative excess production of either α chains or β chains, which without their partner chains are unstable and precipitate in RBCs or their precursors. The inclusion bodies produced by this process increase the rigidity of RBCs and result in their destruction, either in the marrow or the circulation or both. Hence the anaemia of thalassemia results from ineffective erythropoiesis due to intramedullary RBC destruction, and a shortened RBC survival caused by haemolysis.

Thalassemias are classified, according to the particular globin chain that is ineffectively produced (Table 15). In α *thalassemia* there is reduced rate of chains synthesis. β *thalassemias* are associated with a deficiency of β chains.

In β thalassemias, a chain synthesis continues beyond the neonatal period, and most patients have an increased proportion of HbF ($\alpha_2\gamma_2$). In α thalassemia, the imbalance produces an excess of β chains, which form β tetramers (HbH), in adult life, and an excess of γ chain, which form γ tetramers (HbBart's) in infancy.

Molecular Basis of the Thalassemias

Molecular biology has provided an understanding of the nature of the defects in thalassemia syndromes. There are two a genes present on each chromosome 16 – a_1 and a_2. The β genes are located on chromosome 11 alongside the g and d genes. A large number of molecular defects are associated with a thalassemia phenotype, most of the defects in β thalassemia are small, often single base- pair changes.

There is marked phenotype variation in this condition because of heterogeneity at the molecular level. Some patients have mutations that result in failure to produce any globin chain (β^o mutations), whereas other mutations allow globin chain production at a reduced rate (b^o mutations). In α thalassemia, gene deletions are the most common molecular defects, but, because any individual inherits four genes, there are broadly four phenotypes corresponding to deletion of one, two, three or four genes.

β - Thalassemias

Occur predominantly in Mediterranean region and Middle and Far East. Clinically, β thalassemia is a condition of variable severity, ranging from the most severe thalassemias (associated with $w\beta^o$ mutations), to the mild heterozygous forms in which the patients have mild microcytic hypochromic anaemia.

β-thalassemia Major – (Homozygous β-thalassemia)

Special tests for diagnosis.

- HbF levels are high since γ-chain synthesis continues in absence of β-cell formation.
- Hb electrophoresis – demonstrates bands of both HbA and HbF in β-thalassemia.
- Globin chain synthesis show lack of synthesis of β-chains hence a:b globin chain synthesis ratio is altered (normal 1:1).
- DNA analysis is useful in assessing the severity of the disease and diagnosis.
- Biomagnetic liver spectrometry evaluates haemosiderosis of the liver.

Table 15: Classification of thalassemias.

β-thalassemia	*α-thalassemia*	*Misc. thalassemia syndromes*
Thalassemia major	Hydrops foetalis	HB-S Thalassemia
Thalassemia intermedia	HbH disease	HbE - Thalassemia
Thalassemia trait	Thalassemia trait	HbD - Thalassemia
	αβ-Thalassemia	HPFH- Hereditary persistency of foetal haemoglobin

Pathophysiology of β-thalassemia

1. *Accumulation of free α-chains* in normoblasts which fail to mature and die in the marrow (apoptosis) which results in ineffective haemopoiesis.
2. *Extravascular haemolysis* – Red cells formed from abnormal normoblasts are destroyed in the spleen causing haemolytic anaemia.
3. *Changes in bone marrow and bones* – Development of anaemia due to short red cell survival, stimulates EPO production which acts on bone marrow leading to erythroid hyperplasia of bone marrow causing expansion of medullary cavities of bones, widening of both outer and inner tables of the skull and of long bones.
4. *Extramedullary haemopoiesis* causes hepatosplenomegaly.
5. *Iron overload* is due to haemolysis of RBCs, increased absorption of iron from GI tract, repeated blood transfusions. Iron gets deposited in endocrines, liver, heart, bone marrow, spleen, pituitary and islets of Langerhans.

Clinical Features

1. *Onset* – Affected children fail to thrive from about third month and become progressively more anaemic.
2. *Increasing pallor*
3. *Splenomegaly* – Haem siderosis with extramedullary haematopoiesis
4. *Facies* – Frontal bossing due to thickening of cranial bones and prominent cheek bones due to overgrowth of zygomatic bones.
5. *Mild haemolytic jaundice*
6. *Bone changes* – X-ray shows expansion of diploe with thinning of outer and inner tables. 'Hair on end' appearance due striations at right angles to inner table (Fig. 20). X-rays of metacarpals and metatarsals and phalanges show a 'mosaic' pattern because of trabeculations.
7. *Increased susceptibility to infections*
8. *Hepatomegaly* – Due to extramedullary haemopoiesis in first 3-4 years. Later on further enlargement due to haemosiderin deposits in Kupffer cells.
9. *Cardiac involvement* – Myocardial haemosiderosis may result in arrhythmias and cardiac failure.
10. *Endocrines*
    - Stunted growth from GH deficiency
    - Delayed puberty due to hypothyroidism
    - Hypoparathyroidism can cause osteoporosis and fractures
    - Diabetes mellitus due to iron deposits in islets of Langerhans

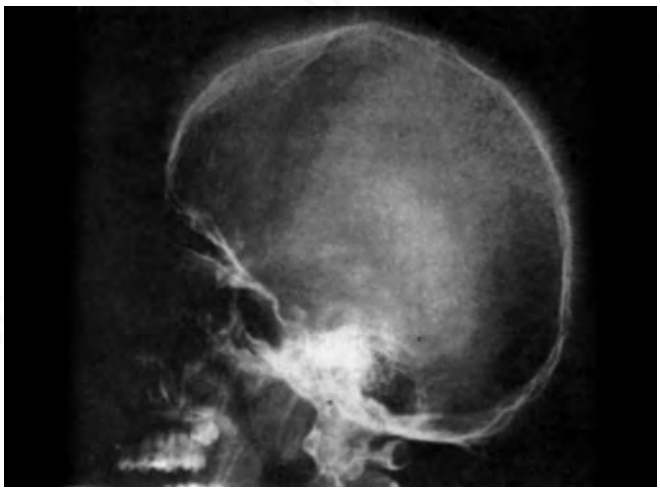


Fig. 20: The skull in thalassemia showing the 'hair-on-end' appearance of skull vault. Such appearance can occur in -1. Other haemolytic anaemias such as sickle cell disease, hereditary spherocytosis, elliptocytosis, and in pyruvate kinase deficiency. 2. Neoplasms – Neuroblastoma metastasis, hemangioma, plasmocytoma. Rarely meningioma and osteosarcoma. 3. Miscellaneous – Cyanotic congenital heart disease, severe iron deficiency anaemia in childhood.

Investigations

1. *Haematological*
    - Anaemia – Moderate to severe with 10-12 gm/dl. RBCs are microcytic hypochromic. Target cells are present and basophilic stippling is common. Also presence of tear drop, elliptical, fragments in red cells and at times red cell with Howell Jolly body (Fig. 21).

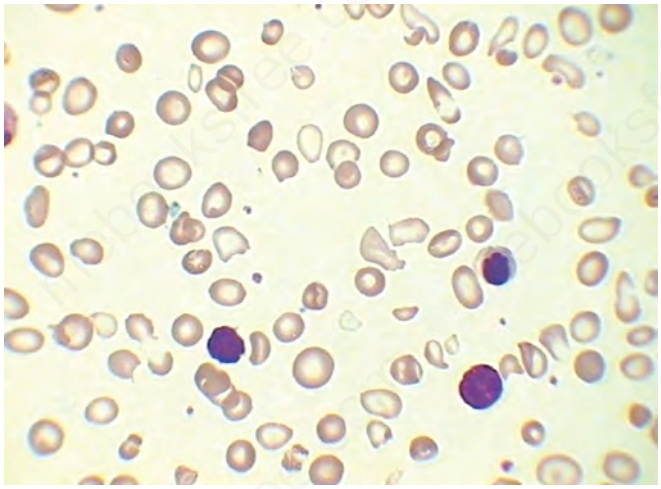


Fig. 21: Thalassemia major showing microcytic hypochromic cells, nucleated RBC and anisopoikilocytosis

- Reticulocytosis
- Leucocytosis with few metamyelocytes and myelocytes

2. *Biochemical*
   - Reduced serum haptoglobins
   - Bilirubin (unconjugated) increased and urine urobilinogen increased
   - Iron status – (a) Serum iron and ferritin markedly increased. (b) Total iron binding capacity (TIBC) reduced.
3. *Bone marrow*
   - Erythroid hyperplasia with reversed M:E ratio
   - Normoblastic erythropoiesis
   - Ineffective erythropoiesis – Some normoblasts die in the marrow without maturing into red cells
   - Myelopoiesis and Megakaryopoiesis
   - Increased bone marrow iron

Other special tests:

1. HbF levels are high.
2. Hb electrophoresis – Bands of both HbA and HbF in β-thalassemia.
3. Global chain synthesis – α–β globin chain synthesis ratio altered (normal l:l) due to lack of synthesis of β chains.
4. DNA analysis – useful for predicting disease severity and diagnosis.
5. Liver spectrometry for detecting haemosiderosis of liver.

Management

1. *Blood transfusions* to keep Hb between 9-11 gm%, if infant's Hb. 6-7 gm% and failure to thrive. Transfusions are given every 2-4 weeks.
2. *Iron chelation* – (a) Desferrioxamine (DFX) as S.C. infusion using a syringe driver pump/infuser.
   Indications – (a) S. ferritin level > 200 mg/L. (b) Deferiprone orally is fairly well tolerated. S. ferritin needs monitoring. (c) Deferasirox orally, if Deferiprone is not given because of side-effects.
   Side-effects include arthralgia, anorexia, liver dysfunction.
3. *Splenectomy* – Hypersplenism due to splenomegaly causes neutropenia and increased need for blood transfusion. Splenectomy reduces severity of neutropenia and subsequent infections.
4. *Bone marrow transplantation* – Indication for BMT is in cases where matched siblings are available in a family, if not available, to look for a matched related donor. This is curative for the patient.

Prevention of Thalassemia Major

1. *Thalassemia trait in parents* – If antenatal check up reveals trait (by assessing HbA_2 levels (4-8%), then father should be assessed for thalassemia trait and, if positive then CVS (chronic villous sampling) is necessary.
2. *Antenatal VS* – at 9-10 weeks of gestation analysis of foetal DNA. If foetus is homozygous for thalassemia, termination of pregnancy is advisable.
3. *Thalassemia screening* – All mothers with Hb < 11gm% during their first antenatal check-up should be screened for Hb estimation. If MCV < 70 fl, MCH < 23 and RBC count of 7.5 million. If HbA_2 estimation 4-8% a diagnosis of thalassemia trait is suggested.

Thalassemia Intermedia

Patients who inherit mutations which lead to only mild reduction in β chain synthesis have a much less severe disorder. They are usually not transfusion dependent, though splenomegaly and hypersplenism may warrant splenectomy.

Heterozygous β-thalassemia (β-thalassemia trait)

Those affected are usually asymptomatic and diagnosis is made on discovery of hypochromic anaemia in absence of iron deficiency or other causes. Mild to moderate splenomegaly in about one-third. HbA_2 elevated.

Diagnosis of Thalassemia Trait

1. *Nestroft test* – is naked eye red cell osmotic fragility test. In case of positive test, HbA_2 estimation is done for confirmation.
2. *HbA_2 estimation* is 4-8% and is carried out by HPLC.

α-thalassemia

Clinical phenotypes:

i. α-Thalassemia-2 trait - Single gene deletions – (Silent carrier state).
ii. α-Thalassemia-1 trait – Two copies of the gene are deleted. Mild hypochromic microcytic anaemia.
iii. ***Haemoglobin H disease*** – Three copies of the gene are deleted. Characterised by variable degree of anaemia with splenomegaly and typical thalassemic blood picture. *Diagnosis* confirmed by Hb electrophoresis which shows variable amounts of HbH. *Management* – Symptomatic with blood transfusions, use of haematinics and judicious use of splenectomy and iron-chelating agents.

iv. ***Haemoglobin bart's hydrops syndrome*** – results from deletion of all four α genes and is a common cause of stillbirth in some races. Affected babies have total absence of α chain synthesis and produce largely HbBart's hydrops foetalis.

v. ***Haemoglobin constant spring*** (HbCS) – Single base mutation results in formation of elongated α chains, and an abnormal Hb (HbCS). Clinical picture similar to haemoglobin H disease.

C. DISORDERS OF RED CELL MEMBRANE

1. ***Hereditary Spherocytosis*** – Haemolytic anaemia associated with intermittent jaundice and splenomegaly. Complications include haemolytic or aplastic crises related to infection, gallstone formation, development of haemochromatosis, and chronic leg ulceration. *Diagnosis* – Many spherocytes on blood film. Increased red cell osmotic fragility. *Treatment* – Splenectomy.
2. ***Hereditary Elliptocytosis*** – Symptomless or may be associated with haemolytic anaemia and splenomegaly. Diagnosis by presence of more than 25% oval red cells in peripheral blood. *Tr.*–Splenectomy is indicated in patients who have symptoms.
3. ***Acanthocytosis*** – Red cells with spikes found in association with total absence of β lipoprotein. Presence of malabsorption, CNS involvement and retinitis pigmentosa. Anaemia absent or mild.
4. ***Stomatocytosis*** – Red cells with a staining pattern in which there is a gap in the middle of the cell (resembling a mouth). Sodium influx produces a swollen water-loaded cell which is destroyed in the spleen leading to haemolytic anaemia. Splenectomy of benefit in a severe case.

II. ACQUIRED HAEMOLYTIC ANAEMIAS (DUE TO EXTRACORPUSCULAR DEFECT).

A. Immune Haemolytic Anaemias

1. ***Haemolytic disease of the new born:*** The term 'isoimmune haemolytic disease of the newborn' is used to describe a group of conditions resulting from the transplacental transfer of maternal blood group antibodies capable of destroying the infant's red cells.

   The condition generally results from the passage of antibodies of the rhesus (anti-D, anti-C, anti-E) or ABO blood groups systems.

   Rhesus iso-immune disease affects Rh-positive foetuses of Rh-negative mothers, but requires a previous sensitizing agent. This is usually the transplacental passage of foetal red cells into the maternal circulation during a previous pregnancy, but may also result from transfusion of Rh-positive blood. The most prevalent antibody is anti-D, despite, the use of anti-D prophylaxis. Other antibodies (e.g. anti-Kell) can be responsible.

   Haemolytic disease involving the ABO group system does not require prior sensitization, because anti-A and anti-D antibodies occur naturally. Although these account for about 50% of all cases of neonatal haemolytic disease, the clinical pattern is much less severe than that caused by rhesus incompatibility.

2. ***ABO incompatibility***: Spontaneously occurring IgG isoantibodies may appear within the ABO blood group system from previous isoimmunisation or for no obvious reason. ABO incompatibility is responsible for about half of all cases of neonatal haemolytic disease. ABO incompatibility rarely causes dangerous neonatal haemolysis.

Clinical Features

I. **Haemolytic disease of the foetus**

   a. *Macerated foetus.*

   b. *Hydrops foetalis* – Severe oedema, pallor, yellow vernix, hepatosplenomegaly and petechial bleeding. The foetus usually dies in utero about 6 weeks before term or may die within a few hours after birth.

II. **Haemolytic disease of the newborn**

   1. *Icterus gravis neonatorum* – The baby is not born jaundiced but becomes so within a few hours of birth. Jaundice reaches a maximum by the third or fourth day. At bilirubin levels of 20 mg/100 ml (345 μmol/litre) or more kernicterus may develop with lethargy, hypotonia and poor feeding. This goes on to a state characterised by head retraction and generalized hypertonia. Mild cases may survive to develop the post-kernicterus syndrome of athetoid cerebral palsy, nerve deafness and dental enamel dysplasia.
   2. *Haemolytic anaemia* – Mildest form of the disease due to only slight sensitization of the mother. Mild neonatal icterus may be present.

Management

a. ***Intrauterine foetal transfusion*** – Haemolysis of foetal blood is accompanied by production of bilirubin

which passes into the amniotic fluid which can be obtained for examination by paracentesis. Increased levels of bile pigment in the fluid, or high level with no evidence of fall on subsequent investigation indicates severe haemolytic disease. It is not safe to induce labour before 34-36 weeks, and if treatment is required as indicated by amniocentesis, intrauterine transfusion should be attempted. This is carried out between 24 and 36 weeks and is repeated every 10-20 days until the foetus is considered to be viable.

b. ***Exchange transfusion*** – At birth cord blood should be taken for estimation of Hb and bilirubin levels. An Hb level 12g/dl or less, or bilirubin of 75 mmol/litre or more, indicates need for exchange transfusion. The principle of exchange transfusion is based on the alternate injection and withdrawal of blood from the infant.

c. ***Phototherapy*** – reduces hyperbilirubinemia associated with haemolysis. It is useful when bilirubin is rising slowly and may reduce need for subsequent exchange transfusions.

Monitoring

For those at risk from haemolytic disease of the newborn. (a) *Maternal antibody levels*– Screen mothers at first antenatal visit and again at 30 weeks. In affected mothers, the antibody levels indicate when foetal blood sampling is required. (b) *Amniotic fluid bilirubin* – Optical density of amniotic fluid at 450 nm reflects the amount of bilirubin present. A rising value indicates severe haemolysis and impending hydrops foetalis. (c) *Foetal blood sampling* – allows measurement of haemoglobin blood group antigens and antiglobulin (Coomb's test). (d) *Ultrasound* – is not a reliable predictor of hydrops foetalis.

Quantity of blood exchanged – 80 ml per lb of body weight i.e. twice the expected blood volume of the patient. Therapy of choice both for correction of anaemia and for control of hyperbilirubinemia. *Indications* – Prematurity, history of severe erythroblastosis or kernicterus in previous siblings, development of signs of central nervous system involvement, hypoalbuminemia, or a level of Hb of 12 g/100 ml (12 g/decilitre) or under, or a bilirubin level of 4 mg/100 ml (68 µmol/litre) or more. Repeated transfusions may be necessary to maintain level of serum bilirubin at less than 20 mg per 100 ml. In case of ABO incompatibility fresh group O blood of the same Rh (D) group should be used.

The mother should not be permitted to nurse the infant with erythroblastosis, because anti-Rh agglutinins have been found in breast milk.

Prevention

It is possible to prevent sensitization of an Rh negative mother by administering anti-D (Rh) immunoglobulin 100 µg 1M within 72 hours after delivery of an Rh positive baby. A Kleihauer test should be performed on the mother's blood and, if foetal cells are detected at a frequency of more than 1 in 600, further anti-D should be given. Anti-D should also be given to Rh-negative females after abortion for threatened ante-partum haemorrhage and obstetrics manoeuvres, or other traumatic event during pregnancy. 50 µg is given before 20th week of pregnancy, and after this 100 µg.

3. ***Autoimmune haemolytic anaemia*** (AIHA) – can be classified according to whether the antibody reacts with red cells best at body temperature (warm antibodies) or at lower temperatures (cold antibodies).

   a. *Warm antibody haemolytic anaemia* – Most patients have autoantibodies of the IgG class on their cells. About half the patients have underlying disease such as lymphoma, chronic lymphocytic leukaemia, SLE, or ovarian malignancies. *Clinical picture* – ranges from mild haemolysis to life-threatening anaemia. Patient is jaundiced and may have splenomegaly. *Diagnosis* – Blood film shows polychromasia with spherocytes and reticulocytosis. Positive Coomb's test. IgG can be detected in about 50% of cases. *Treatment* – Steroids IV in severely ill patients, oral prednisolone 60 mg/day for mild cases, later dose is reduced to that which will maintain an adequate Hb level; if this fails splenectomy. If both these fail immunosuppressive therapy with azathioprine or cyclophosphamide or IG intramuscular.

   b. *Cryopathic haemolytic syndromes* – (Cold immune haemolytic anaemias) – There are 2 disorders in which increased red cell destruction occurs at temperatures below normal body temperature:

      i. Cold agglutinin disease – A marked elevation of cold agglutinins may occur either transiently in association with mycoplasma pneumoniae and infectious mononucleosis or more persistently as part of idiopathic cold agglutinin disorder of old age, or in association with neoplasms particularly reticuloses. *Clinical picture* – is variable. In acute variety – caused by Mycoplasma infection there is a brisk haemolytic episode with haemoglobinuria 2 to 3 weeks after a short respiratory illness. In chronic idiopathic form – anaemia with Raynaud's phenomena and

occasional haemoglobinuria. It has anti-I antibody, of IgM type. It reacts stongly with RBCs at lower temperature, so hemolysis takes place when person is exposed to cold. *Diagnosis* – Cold agglutinin titre markedly raised, positive direct Coomb's test, protein electrophoresis usually shows a 'monoclonal' IgM band. *Treatment* – Patient should wear warm clothing and avoid cold weather. Chemotherapy, if underlying lymphoma.

ii. Paroxysmal cold haemoglobinuria – Rare disease characterised by intermittent attacks of intravascular haemolysis and haemoglobinuria. It's self limited. It has anti-P specific antibody, called Donath-Landsteiner antiobody. It reacts with RBCs at low temperature 4°C, but when temperature shifts to 37°C hemolysis takes place in presence of complements. There are two forms of the disease – (i) Chronic relapsing illness associated with congenital syphilis (now extremely rare). (ii) Acute transient variety which may be precipitated by virus infection such as mumps or measles. Severely anaemic patients may require transfusion.

4. ***Drug-induced autoimmune haemolytic anaemia***– One of three mechanisms – (a) Innocent bystander – Antibody develops against the drug which forms a complex with it, and this attaches to the red cell membrane. Complement is then bound and causes destruction of the red cell, e.g. quinine. (b) Drug acts as hapten – Drug binds firmly to red cell membrane and antibody is formed with specificity for the drug-membrane complex, e.g. penicillin. (c) True autoimmune haemolytic anaemia, e.g. methyldopa, levodopa, procainamide, mefenamic acid.

B. Non-immune acquired haemolytic anaemias

1. Due to trauma to red cells

a. *Microangiopathic haemolytic anaemia* –characterized by intravascular haemolysis and fragmentation and distortion of red cells caused by disease of small vessels. *Types* – (i) Haemolytic uremic syndrome – Acute haemolytic anaemia with renal failure in infancy and childhood. (ii) Malignant disease – Disseminated mucus-secreting carcinomas, particularly of stomach. (iii) Thrombotic thrombocytopenic purpura – Acute haemolytic disorder with neurological and renal manifestations. In addition there is generalized purpura and haemoglobinuria. (iv) Other disorders – DIC, collagen vascular disorders, toxaemia of pregnancy, septicaemia, purpura fulminans and malignant hypertension.

b. *Cardiac haemolytic anaemia* – Abnormal turbulence caused by repair or replacement of aortic or mitral valve, or teflon-patch repair of septal defects, or severe AR or AS. Patient develops moderate to severe intravascular haemolysis with haemoglobinuria and haemosiderinuria. Iron deficiency may result from iron loss through the kidneys.

c. *March haemoglobinuria* – A condition characterised by attacks of haemoglobinuria following strenuous physical exercise. A similar picture has been described in those who practise karate.

2. **Resulting from infection**

a. *Septicaemia* – Haemolytic mechanisms vary. Treatment consists of control of underlying infection and blood transfusion.

b. *Parasitaemia* – e.g. malaria or Bartonella bacilliformis.

c. *Other infections* – Leishmaniasis, cholera, toxoplasmosis. Occasionally viral infections such as mumps and infectious mononucleosis.

3. **Due to chemicals and toxins:**

a. *Heavy metals* – Lead poisoning (Lead also interferes with Hb synthesis).

b. *Gases* – Inhalation of arsine gas (workers in metal-refining industries).

c. *Sodium or potassium chlorate.*

d. *Physical agents* – anaemia due to 100% oxygen inhalation in astronauts.

e. *Insect stings and snake bite.*

4. **Acquired defects of the red cell membrane**

a. *Liver disease* – Red cell survival may be shortened, the degree of haemolysis is usually mild. Occasionally acute haemolysis with upper abdominal pain may occur in alcoholics with liver disease, usually after a bout of drinking (Zieve's syndrome).

b. *Paroxysmal nocturnal haemoglobiuria (PNH)* – occurs usually in third to fifth decade and is characterised by chronic intravascular haemolysis with exacerbations (typically in the morning), haemoglobinuria and a thrombotic

tendency. Diagnosis – Complement fixation tests. Treatment – Eculizumab block breakdown of red cells. Bone marrow transplant can prove curative.

4. BONE MARROW FAILURE

NORMAL MARROW FUNCTION

The normal adult marrow produces about 1.7×10^{11} red cells (17 ml), 1.0×10^{11} neutrophils and 2×10^{11} platelets each day. All peripheral cells arise from common progenitor cells known as pluripotent stem cells. An important property of these cells is selfrenewal, which ensures a continuous supply throughout life. Each pluripotent cell is capable of producing an individual clone consisting of a number of red cells, granulocytes, platelets and lymphocytes, together with their intermediate progenitor cells.

The term 'bone marrow failure' encompasses conditions in which there is a primary failure, at the haemopoietic precursor level, to produce one or more of the circulating blood cell lineages. The term usually excludes pancytopenia associated with marrow infiltration (as in acute leukaemia) and those that arise predominantly from peripheral destruction. Bone marrow failure may be inherited or acquired. Bone Marrow failure syndromes are listed in Table 16.

APLASTIC ANAEMIA

Aplastic anaemia (AA) is a group of disorders in which haemopoietic cells of bone marrow are replaced by fat resulting in progressive cytopenia. Causes of aplastic anaemia are enumerated in Table 17.

Severity of acquired aplastic anaemia is determined from peripheral blood and bone marrow examination as given in Table 18.

Clinical Features

Onset – Insidious, sometimes abrupt onset and course.

1. *Symptoms due* to *anaemia* – Weakness, fatigability, lassitude, dyspnoea on exertion.
2. *Symptoms due* to *thrombocytopenia* – Bleeding into skin either as ecchymoses or petechiae, epistaxis, menorrhagia, bleeding from gums and alimentary tract. Rarely cerebral haemorrhage. Presence of spontaneous bleeding indicates severe marrow failure with platelet counts below 20×10^9/litre.

Table 16: Bone marrow failure syndromes.

Inherited
Neutropenia
• Fanconi's anaemia
• Pancytopenia
• Dyskeratosis congenita
• Shwachman Diamond syndrome
• Pearson's syndrome
• Reticular dysgenesis
• Amegakaryocytic thrombocytopenia
Single cell cytopenia
• Red cell aplasia
– Diamond-Blackfan syndrome
• Neutropenia
• Kostmann syndrome
– Shwachman Diamond syndrome
– Reticular genesis
• Thrombocytopenia
• Amegakaryocytic thrombocytopenia with absent radii (TAR)
Acquired
• Aplastic anaemia
• Pure red cell aplasia
• Others
Congenital dyserythropoietic anaemias
Myelodysplastic syndromes
Sideroblastic anaemia
Porphyrias
Leukemias

3. *Symptoms due* to *neutropenia* – Fatigue, sore throat, ulceration of mouth and pharynx, fever with chills, sweating. Chronic skin infection, recurrent chest infections, with severe neutropenia and risk of overwhelming septicaemia.

Abnormalities associated with Fanconi's anaemia – Short stature, hyper-pigmentation of skin, malformation of skeleton, microsomy, macrocephaly, malformation of kidneys, mental retardation, cryptorchism.

Laboratory Investigations

Peripheral blood – shows anaemia, neutropenia. Also reticulocytopenia.

- Typically large size RBCs and commonly increase in MCV. Low reticulocyte count. Some variation in RBC size and shape; however extreme abnormalities suggest

Table 17: Causes of aplastic anaemia.

• Idiopathic in about 2/3 of patients
• Physical agents ionizing radiation
• Viruses: Viral hepatitis
• Drugs
Antibiotic and anti-infective
Chloramphenicol
Cotrimoxazole
Nitrofurantoin
NSAIDs
• Diclofenac
• Indomethacin
Anti-thyroid
• Carbimazole
• Methimazole
Anticonvulsant
• Phenytoin
Psychotropic
• Phenothiazine
Antirheumatic
• D-penicillamine
• Gold salts
Cytotoxic agents
• Vincristine
• Methotrexate
• Adriamycin
Chemicals
Benzene
Arsenic

possibility of hypoplastic myelodysplastic syndrome (MDS) or presence of a clone of paroxysmal nocturnal haemoglobinuria (PNH) cells. Presence of nucleated RBCs also raise possibility of PNH or MDS.

- Lymphocytic count normal or reduced, but morphology normal except for increased granulation (so-called toxic granules).
- Abnormal cells (including blasts and hairy cells) must be sought – these cells are absent in aplastic anaemia.

Bone Marrow

a. *Bone marrow aspirate* is usually a dry tap or marrow fragments are obtained which demonstrate – (i) Marked hypocellularity with replacement of marrow cells by fat, focal areas of haemopoiesis are present in initial stages. (ii) Paucity of erythroid, myeloid and megakaryocytic precursors. (iii) Lymphocytes and plasma cells predominate. (iv) Stem cell pool reduced to ≤ 1% of normal at time of presentation in severe cases.

b. *Bone marrow trephine biopsy* – (i) Marked reduction in cellularity, replacement by fat which is infiltrated by lymphocytes and plasma cells. (ii) Increase in mast cells. (iii) Increased bone marrow iron (Fig. 22).

Table 18: Severity of acquired aplastic anaemia.

	Peripheral blood	*Bone marrow*
Very severe	• Neutrophils < 0.2×10^9/L	• 25% normal cellularity
	• Platelets < 20×10^9/L	• Moderately hypocellular (<30 of remaining cells haemopoietic)
	• Reticulocytes < 20×10^9/L	
	• Transfusion dependent	
Severe	• Neutrophils 0.5×10^9/L	• As for very severe
	• Otherwise as for very severe	
Non-severe	• Neutrophils 0.5-1.5 $\times 10^9$/litre	
	• Platelets 20-100 $\times 10^9$/litre	• Hypocellular
	• Reticulocytes 20-60 $\times 10^9$/litre	

Management

1. ***Supportive care with blood products***
   - Packed red cells for anaemia
   - Platelets for thrombocytopenia
   - G-CSF/GM-CSF to increase neutrophil count
2. ***Control of infection*** – Opportunistic infections (particularly bacterial or fungal) may occur in patients with neutrophil counts of < 0.2×10^9/L (ANC < 1500). Such patients should be isolated with prophylactic antibiotics, particularly against fungal and Gram-negative infections.
3. ***Restoration of marrow activity***

Immunosuppressive therapy – has been found effective in producing remission in aplastic anaemia. The most effective agent is antithymocyte globulin (ATG) or antilymphocyte globulin (ALG).

ATG is given IV into central vein over 12-16 hours daily for 5 days. Fever, rigor and rashes are common during first 2 days, and serum sickness may occur 7-10 days later. Two-thirds of patients achieve remission. Methylprednisolone is administered with ATG to avoid immune reaction against heterologous globulin.

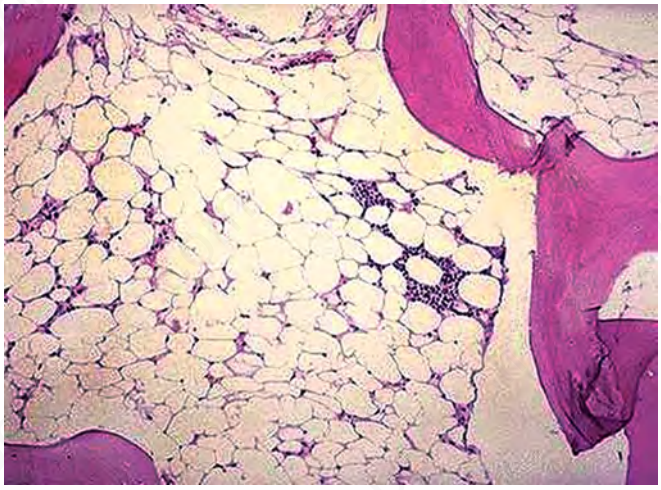


Fig. 22: Bone marrow in a patient with aplastic anemia. Notice there are very few cells except for the fat cells

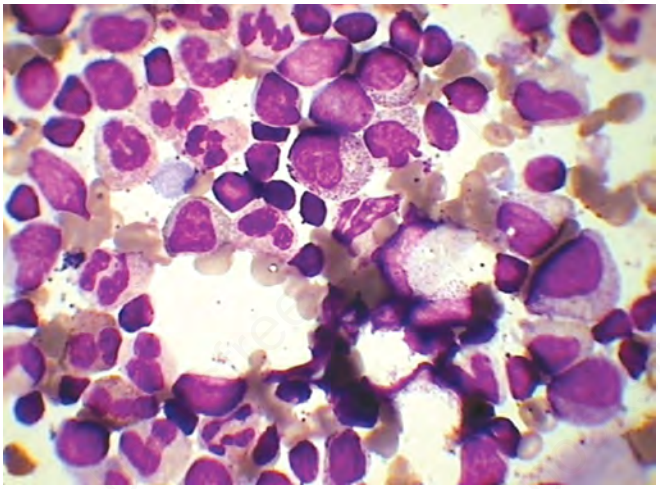


Fig. 23: Bone marrow aspirate from a case of pure red cell aplasia showing normal myeloid precursors with marked paucity of erythroid precursors

Addition of cyclosporine to ATG may increase the likelihood of remission, particularly in patients with severe aplastic anemia. Immunosuppressive therapy is most effective in patients with non-severe aplastic anaemia. If the first course fails to produce a response at 4-6 months, a second course may be given.

Stem cell transplantation – *Allogenic bone marrow transplantation* is an effective means of curing the disease. Results are best seen in children and young adults with severe aplastic anaemia and in older adults with very severe disease.

Stem cells mobilized in the peripheral blood following treatment of the donor with granulocyte stimulating factor (G-CSF) are an equally effective source but bone marrow harvest of stem cells is preferred due to common incidence of GVHD.

Conditioning of stem cell transplantation is with AGL and cyclophosphamide. Cyclosporine is used with methotrexate post-transplantation to reduce the incidence of graft failure and graft-versus host disease. Successful results are achieved in about 80% of patients.

Neutropenia

Neutropenia is the term used when neutrophil count is $<1.5 \times 10^9$/L. Neutropenia is caused by (a) Suppression of myelopoiesis. (b) Peripheral destruction. (c) Peripheral pooling. Causes of Neutropenia (agranulocytosis) are listed in Table 19.

2. PURE RED CELL APLASIA

Pure red cell aplasia is an uncommon condition, probably of immune origin, in which RBC precursors are unable to mature to produce reticulocytes and hence mature RBCs.

Causes

Congenital: Blackfan-Diamond syndrome. Anaemia is present from birth or develops within the first year of life and may be associated with other congenital abnormalities. Corticosteroids are effective in some patients; otherwise transfusion remains the mainstay of treatment.

Acquired 1. Autoimmune – SLE, NHL 2. Thymoma associated 3. Viral and bacterial – Hepatitis. Parvovirus B_{19}, EBV associated. 4. Drugs – Phenytoin, azathioprine, anti-TB drugs. 5. Tuberculosis associated. 6. Idiopathic.

Laboratory diagnosis – (a) Peripheral blood – Normocytic, normochromic anaemia with marked reticulocytopenia. Neutropenia with platelet count $<20 \times 10^9$/1. (b) Bone marrow – Almost total absence of erythroid precursors with normal myelopoiesis and megakaryopoiesis in PRCA. (Fig. 23) In parvovirus B_{19} infection smear shows giant proerythroblasts with dog's ears-like cytoplasmic protrusions. Diagnosis parvovirus requires detection of its DNA sequence in blood.

Treatment – RBC transfusions till marrow recovers. If no response, long term transfusion with regular iron chelation. Thymectomy for thymoma. Corticosteroids with addition of azathioprine. Cyclosporine may be useful in resistant cases. For persistent parvovirus B_{19}, intravenous immunoglobulin therapy advocated (Dose- 0.4 mg/kg/day for 5 days).

Table 19: Causes of neutropenia (agranulocytosis).

Drug-induced
Antibacterial
• Chloramphenicol
• Cotrimoxazole
• Doxycycline
• Ciprofloxacin
• Cephalosporins
• Gentamycin
• Nitrofurantoin
Anti-inflammatory
• Phenylbutazone
• Ibuprofen
• Aminopyrine
Antithyroid
• Carbimazole
• Thiouracil
Infections
• Gram negative bacterial septicaemia
• Enteric fever
• Tuberculosis
Viral
• Parvovirus B_{19} infection
• HIV
• Hepatitis B
• EBV infection
• Dengue
Autoimmune diseases
• SLE
• Idiopathic
• Chronic autoimmune neutropenia
Protozoal
• Malaria
• Kala-azar
Miscellaneous
• Radiation
• Felty's syndrome
• Cyclic neutropenia

5. AMEGAKARYOCYTIC THROMBOCYTOPENIA

Thrombocytopenia associated with absence or marked reduction of megakaryocytes in bone marrow, is a rare, chronic condition affecting children and young adults.

Cl. Fs. – Skin purpura, bleeding gums and buccal haemorrhages. Children may present with easy bruising.

Bone marrow examination reveals the diagnosis.

Management – About 1/3 patients slowly develop classical aplastic anaemia, and respond to treatment with antilymphocyte globulin. Another 1/3 progress to MDS (more common in older patients), and ALG is worth trying. The remainder may remain stable for many years, occasionally requiring platelet transfusion.

6. PORPHYRIAS

Porphyrias are a group of inherited or acquired disorders due to a defect in the enzymes of haemosynthesis resulting in accumulation of intermediate products and affecting erythropoiesis.

Types

1. *Hepatic type* – Liver mainly affected. (a) Acute intermittent porphyria. (b) Hereditary coproporphyria. (c) Porphyria cutanea tarda.

   Cl. Fs. (a) Neurological symptoms of rapid onset with high levels of ALA and PBG in blood and urine. (b) Cutaneous sensitivity to sunlight.

2. *Erythropoietic type* – Cutaneous photosensitivity is main clinical manifestation.

7. DISORDERS OF HAEMOSTASIS

Haemostasis is a tightly regulated homeostatic mechanism that maintains blood flow under physiological conditions and permits rapid, localized coagulation in the event of tissue damage. A delicate balance exists between four major components – the vascular endothelium, platelets, the coagulation pathway and fibrinolysis.

1. **Endothelium** – Under resting conditions, the endothelium prevents thrombus formation (Fig. 24). It acts as a physical barrier separating haemostatic from reactive endothelial components, and its surface charge may help to repel platelets. It possesses anticoagulant properties attributable to:
   - Constitutional expression of thrombomodulin and heparan sulphate
   - Endogenous synthesis of ectoenzymes, which degrade platelet agonists such as ADP
   - Endogenous synthesis of the vasodilators prostacyclins (PGI_2) and nitric oxide (NO), which inhibit platelet aggregation.

   Tissue damage leads to exposure of the endothelial basement membrane and extracellular matrix. Collagen (principally types I and III), von Willebrand factor and fibronectin promote platelet adhesions to the site of

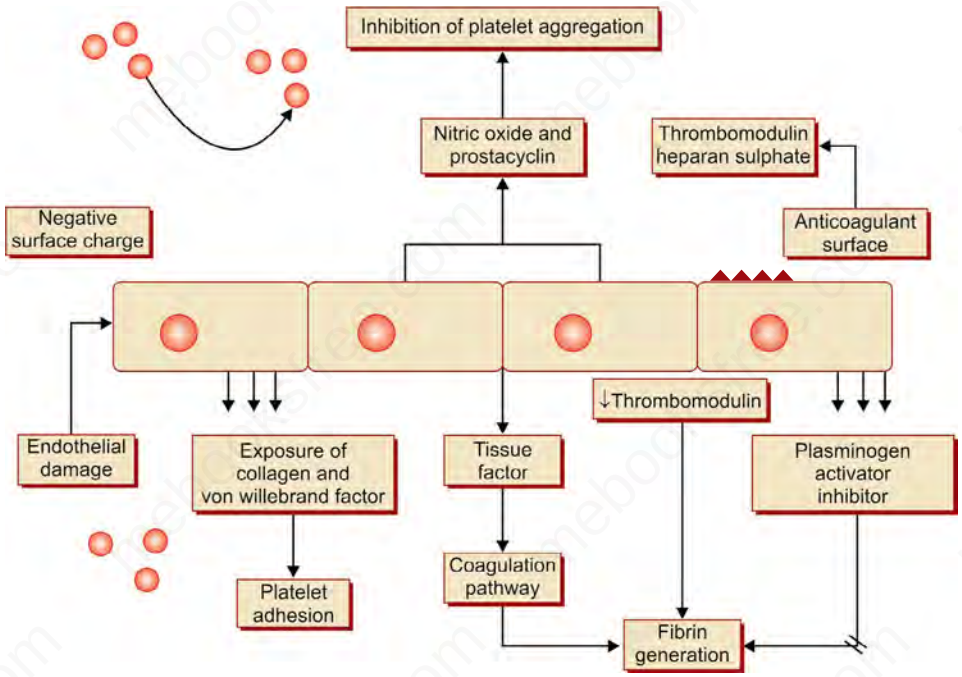


Fig. 24: Endothelial hemostatic function – In the resting state (upper surface), the endothelium functions as an effective anticoagulant. Its negative surface charge repels platelets, and nitrous oxide and prostacyclin inhibits platelet function. Anticoagulant properties are enhanced by surface expression of thrombomodulin and heparan sulphate. However, after stimulation by cytokines or tissue damge, the endothelium rapidly becomes prothromobotic (lower surface). Platelet adhesion is promoted by exposure of subendothelial collagen and von Willebrand factor. Meanwhile, tissue factor secretion initiates fibrin generation and clot formation, while fibrinolysis is inhibited by secretion of plasminogen activator inhibitior, Anticoagulant properties are also modulated by reduced surface expression of surface thrombomodulin

injury, and the endothelium becomes prothrombotic after stimulation by endotoxin or the cytokines interleukin-1 (IL-1), tumour necrosis factor (TNF) and interferon-α. Tissue factor is expressed (initiating the coagulation pathway), fibrinolysis is impaired by secretion of plasminogen activator inhibitor, and surface expression of the anticoagulant thrombomodulin is reduced.

These procoagulant events are regulated to prevent excessive thrombosis by poorly understood mechanisms, endothelial cells secrete tissue plasminogen activator (tPA), initiating fibrinolysis, and thrombin becomes an effective anticoagulant after binding to thrombomodulin.

2. **Platelets** – are an integral component of haemostasis and circulate in close contact with the endothelial cell wall. Adhesion to the cell wall is prevented by high local concentrations of PGI2 and NO, though they attach rapidly following endothelial disruption. In all blood vessels blood flow is faster towards the centre than close to the vessel wall; as a consequence there is a shear effect between adjacent layers of fluid that is maximal nearest the wall-shear forces of 500-5000/second can be attained within arterioles. Under such conditions, the interaction between platelets and von Willebrand factor is vital in mediating irreversible adhesions to damaged endothelium. Under lower flow conditions, collagen, fibronectin and fibrinogen may be able to mediate platelet adhesion independently (Fig. 25).

Adhesion and aggregation – von Willebrand factor is a large, multimeric protein synthesized by the endothelium and secreted into the subendothelium. Following endothelial damage it binds to extracellular collagen, primarily through the A_3 domain. Platelet thethering to exposed thrombogenic surfaces occurs when the platelet glycoprotein GpLb- IX-V complex binds to the A1 domain of von Willebrand factor; this is possible despite rapid flow rates because of the fast association rate of the reaction. The multimeric nature of von Willebrand factor and consequent increased local concentration of A1 binding sites also potentiates adhesion. However, the platelet complex dissociates rapidly, allowing the platelets to continue rolling slowly along the endothelium. During this phase platelets are activated and the platelet GpIIb-IIIa receptor undergoes conformational change, allowing to bind both von Willebrand factor and fibrinogen, and resulting in irreversible platelet adhesion and aggregation, respectively.

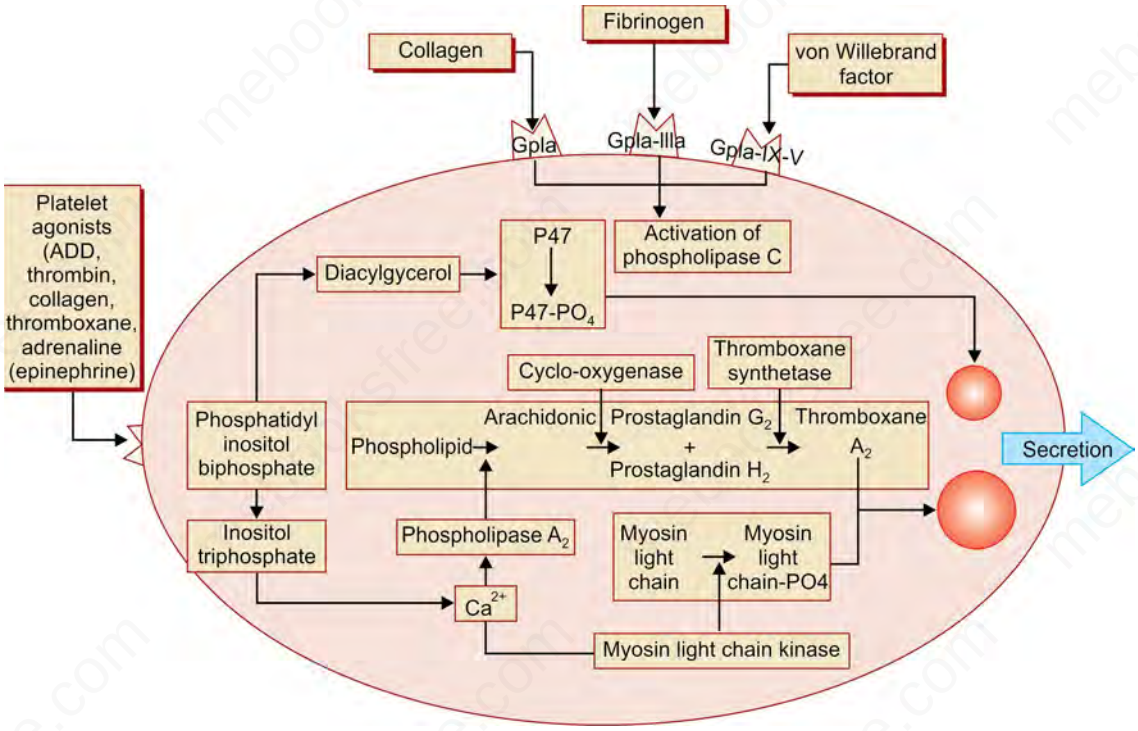


Fig. 25: Platelet function – Specific platelet surface glycoprotein receptors mediate platelet adhesion, aggregation and activation. Platelet adhesion to damaged endothelium is acheived by the binding of von Willebrand factor to the GpIb component of the GpIb-IX–V complex. Aggregation follows,, secondary to bridging of the altered GpIb-IIIa receptors of adjacent platelets by fibrinogen. Other agonists (e.g. ADP, collagen) bind to specific receptors and initiate platelet activation throught activation of phospholipase. C. This enzyme catalyses the cleavage of phosphatidyl inositol biphosphate to inositol triphosphate and diacylglycerol. Diacylglycerol activates protein kinase C, while inositol triphosphate mobilizes calcium ions from the dense tubular system, hence activating phospholipase A_2 and myosin light chain kinase. Phospholipase A_2 liberates arachidonic acid from phospholipid and, via the action of cyclooxygenase and thromboxane synthetase, leads to synthesis of secretion of the thromboxane A_2. With thromboxane A_2, phopholrylated products of myosin light chains and the intracellular protein p47 stimulates secretion of the contents of the dense bodies lysosomes and granules

The dimeric nature of fibrinogen molecule allows inter-platelet bridging and growth of the primary platelet clot.

Activation – Platelet activation is caused by binding to the specific receptors of variousu agonists including thrombin, thromboxane A_2, ADP, collagen and arachidonic acid. Signal transduction is mediated by G proteins and intracellular cAMP; increased cAMP concentrations inhibit platelet adhesion, aggregation and release. Following platelet activation adenylate cyclase activity is reduced and cAMP levels therefore fall. Activation of phospholipase C results, and this cleaves phosphatidyl inositol biphosphate to inositol triphosphate and diacylglycerol. Inositol triphosphate mobilizes calcium; thus many calcium- dependent reactions ensue, including phosphorylation of the myosin light chain, which initiates the contractile reaction of the release mechanism, secretion of platelet granule contents, and liberation of arachidonic acid from membrane phosphatidyl choline.

Platelet activation is accompanied by structural changes. The normal smooth, biconcave disc shape is lost, platelets become spherical with protuberant pseudophilia, and their granules move centrally secondary to activation of the cytoskeletal contractile apparatus secretion follows. Subsequent contraction of cytoskeletal microfibrils may cause clot retraction and promote platelet plug formation. Coagulation is also enhanced by exposure of negatively-charged platelet phospholipids and receptors for specific plasma clotting factors (particularly activated factor V (Va) derived from platelet a granules), which provide the pro-coagulant surface necessary for assembly of the enzyme-cofactor complexes of the coagulation pathway.

Coagulation – It is recognized that the tissue factor – factor VII complex (TF VII) activates both factors IX and X, and that the intrinsic and extrinsic pathways are integrated *in vivo* (Fig. 26).

Factor VII and its cofactor (tissue factor) initiate haemostasis. Tissue factor is a glycoprotein constitutively

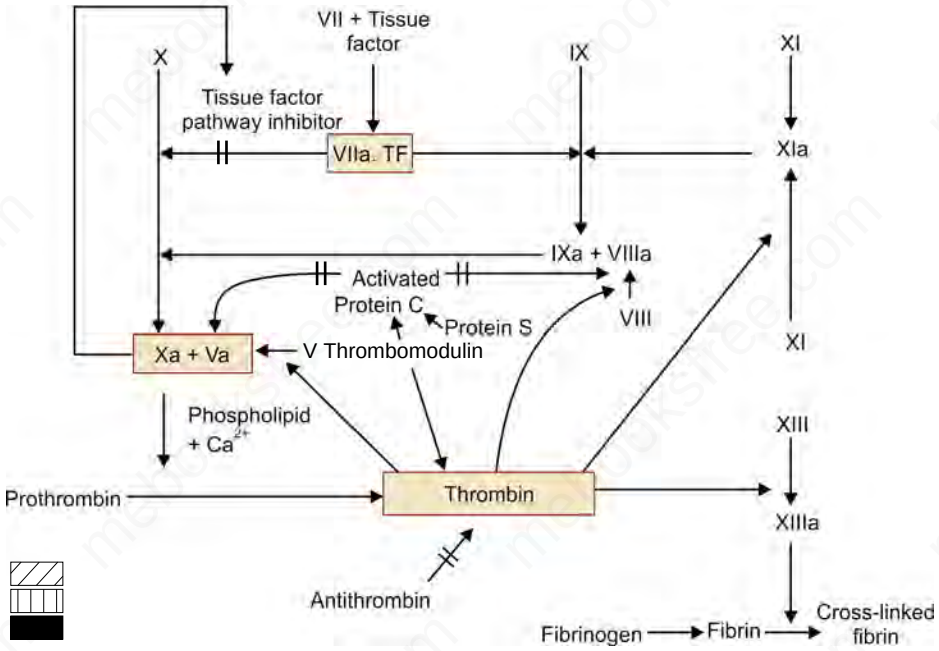


Fig. 26: Hypothesis of blood coagulation – Tissue factor has an integral role in the initiation of coagulation, through activation of factor VII. Activated factor X (Xa) is generated by factor VIIa, tissue factor complex. Because of factor Xa-dependent inactivation of VIIaTF by tissue factor pathway inhibitor, factors IX and XI are required to generate sufficient tenase complex to ensure thrombin generation. The central role of thrombin is shown above. Coagulation is limited by the action of the anticoagulant system

expressed on the surface of fibroblasts; endotoxin II-1 and TNF may induce its synthesis and expression in monocytes, macrophages and endothelial cells. Following endothelial damage, factor VII or Factor VIIa binds to exposed tissue factor, increasing enzymatic activity. This interaction also promotes the ability of trace amounts of factor Xa, (and, less efficiently, factor IXa) to activate factor VII, though it remains unclear how these trace amounts are formed. Small quantities of VIIa are produced continuously under basal conditions, possibly secondary to factor IX activity (basal factor VIIa levels are reduced in haemophilia B). Alternatively, autoactivation of TF.VII might have a role. Once assembled, activated TF.VII (TF. VIIa) activates limited amounts of membrane- bound factors IX and X.

The factor Xa produced initially by this mechanism generates enough thrombin to induce local platelet aggregation and activation of the critical cofactors V and VIII, but is insufficient to sustain haemostasis because of rapid factor Xa dependent inactivation of TF. VIIa by tissue factor pathway inhibitor. Instead, marked amplification is achieved via the action of factors IXa and VIIIa. Factor XIa may be required to produce additional factor IXa, if the amount generated by TF. VIIa is insufficient or fibrinolysis is particularly active. This is consistent with the clinical presentation of factor XI deficiency, in which spontaneous hemorrhage is rare but traumatic and postoperative haemorrhages are relatively common from tissues with high fibrinolytic activity. The precise mechanism of factor XI activation remains unclear but appears to involve thrombin and possibly autoactivation. Although important *in vitro*, the remaining components of the intrinsic system do not appear to have an important haemostatic role.

The tenase complex (factor Xa - factor Va) rapidly converts prothrombin to thrombin. Thrombin hydrolyses arginine-glycine bonds in fibrinogen to form fibrin monomers, and activates factor XIII, which stabilizes the fibrin clot through cross-linkage. It also has a positive feedback role, promoting activation of factor XI and the cofactors V and VIII, and thus ensuring rapid coagulation.

Anticoagulant pathways – Anticoagulants are an integral part of the haemostatic pathway and prevent catastrophic disseminated thrombosis. Antithrombins (serpins) inhibit the serine proteases of the coagulation system, and protein C system neutralizes activated coagulation factors. Although at least serpins have been identified, only antithrombin (formerly antithrombin III) and heparin cofactor II are haemostatically significant. Antithrombin forms a stable 1:1 stoichiometric complex with its substrates (predominantly factor Xa and thrombin). Heparin

promotes antithrombin inactivation of thrombin and factor Xa (the former 2000-fold), thus accounting for its therapeutic efficacy.

Thrombin may bind to surface-bound thrombomodulin, losing its procoagulant properties and becoming a highly effective anticoagulant. Formation of this complex increases the rate of activation of factor C 20,000 -fold. In addition the cofactor protein S forms a Ca^{2+} - dependent complex with protein C, increasing the phospholipid-binding potential and hence activity of protein C. Activated protein C rapidly degrades factors Va and VIIIa and enhances fibrinolysis, thus limiting excessive coagulation.

Fibrinolysis – The primary platelet clot is strengthened by fibrin formation, and tensile strength is further increased by fibrin polymer cross-linking mediated by factor XIIIa. Factor XIIIa also binds antiplasmin to fibrin, and thus may protect the clot against fibrinolysis (Fig. 27). However, fibrinolysis is a prerequisite for normal haemostasis, as shown by the possible thrombotic tendency of patients with plasminogen deficiency. Tissue plasminogen activator (tPA) is released from endothelial cells and converts plasminogen to plasmin (a serine protease). This reaction is promoted when tPA is fibrin-bound and is subject to positive feedback – plasmin cleaves tPA into a two-chain molecule, increasing binding site exposure and promoting complex formation. Plasmin hydrolyses arginine and lysine bonds, resulting in proteolysis of various substrates including fibrinogen, fibrin and factors V, VIII and XIII. Fibrin and fibrinogen cleavage generates fragments X and Y, which inhibit thrombin and fibrin polymerization respectively, in addition to other smaller fibrin degradation products.

Excessive fibrinolysis resulting in fibrinogen consumption and hemorrhage is prevented by inhibition of both tPA and plasmin by plasminogen activation inhibitor and α_2 - antiplasmin.

Plasmin cleaves fibrin, leading to sequential formation of fragments X, Y, D and E, which exhibit positive feedback; hence, fibrinolysis is stimulated once initiated. However, tissue plasminogen activator and plasmin become more

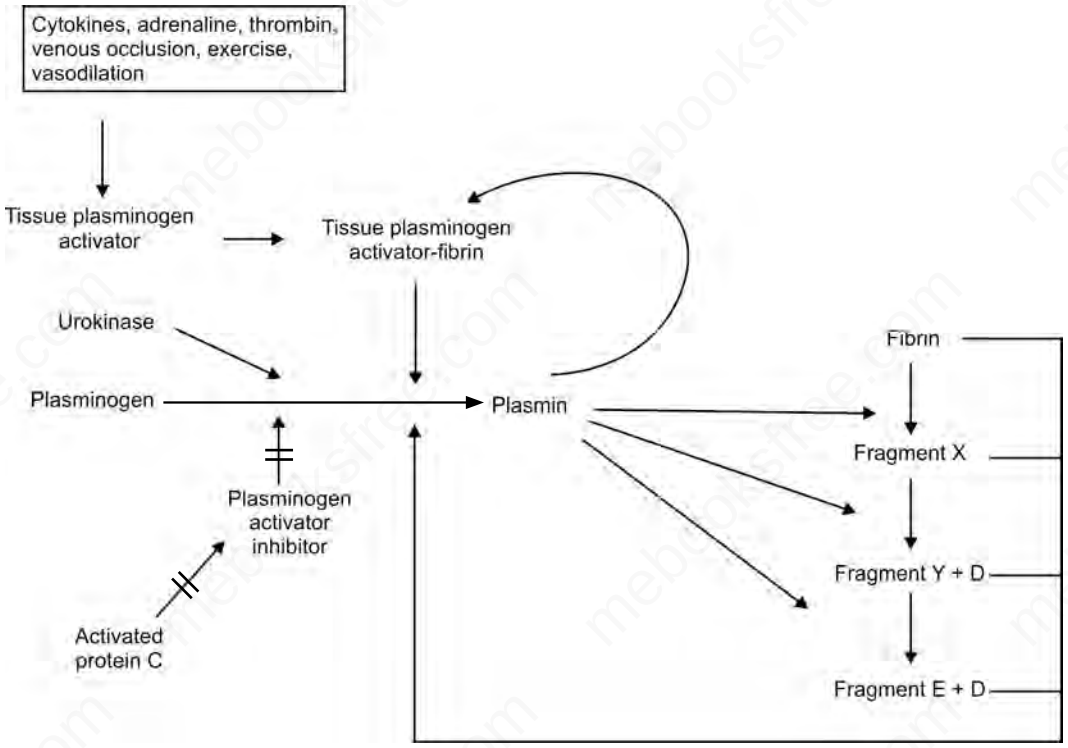


Fig. 27: Fibrinolysis – Tissue plasminogen activator is released from endothelial cells in single–chain form. This has significant proteolytic activity, which is enhanced both by fibrin binding and by plasma binding cleavage to the two-chain from. Plasmin also exerts positive feedback by converting native plasminogen (glutamate plasminogen) to lysine–plasminogen, which has preferential Fibrin binding. This increases plasmin production, localizeds fibrinolysis to the fibirin clot and protects the plasmin generated from inhibition by α–antiplasmin

accessible to their inhibitors as the clot dissolves, and this helps prevent excessive fibrinolysis.

Congenital coagulation disorders – Three diseases haemophilia A, haemophilia, B (Christmas disease) and von Willebrand disease account for more than 90% congenital coagulation disorders, which can cause abnormal bleeding.

HAEMOPHILIA A AND B

Haemophilia A (deficiency of factor VIII c) is about 5 times more common than haemophilia B (deficiency of factor FIX). Both exhibit X-linked inheritance (Haemophilia A due to F8 gene mutation and Haemophilia B due to F9 gene mutation) – all the daughters of patient with haemophilia are carriers of the disease and all the sons are normal. Female carriers may have a sufficiently low factor level to appear as if they have mild haemophilia; this occurs because of extreme ionization. In general, the severity of haemophilia is similar between generations dependent on the resting levels of factor VIII c or FIX (Table 20).

CLINICAL FEATURES

At birth – New born with haemophilia are usually healthy, though bleeding from the cord and cephalohaematoma may occur.

Infant – is usually asymptomatic until 6-12 months, when bruising becomes more obvious. Bleeding from the mouth is common.

During childhood – in severely affected individuals, spontaneous bleeds may occur into the joints and muscles, including the psoas muscle.

Adults – Frequency of spontaneous bleeding usually decreases, but joints may already have been damaged. Intracranial hemorrhage is a life-threatening complication. Spontaneous bleeds are common in mildly affected individuals, but after injury bleeding continues until appropriate therapy is given.

Laboratory investigations – APTT is prolonged in haemophilia A and B, but PT is normal. Specific factor assay demonstrate reduced factor VIII c in haemophilia A and factor IX in haemophilia B. If the clinical history is strongly suggestive of haemophilia, normal APTT does not exclude the diagnosis.

Complications of Haemophilia

1. *Hepatitis* in patients who received multiple transfusion of FFP or cryoprecipitate.
2. *AIDS* in a patient not screened for HIV and treated with FFP or cryoprecipitate.
3. *Anaemia* from excessive bleeding.
4. *Contractures in muscles* following intramuscular hematomas.
5. *Spontaneous intracranial hemorrhage* in severe haemophilia.

Management – Replacement of the missing factor:

Factor VIII dose = (Target Factor VIII levels - Factor VIII baseline levels) × body weight in kg × 0.5 unit/kg (as one unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%).

Factor IX dose = (Target Factor IX levels - Factor IX baseline levels) × body weight in kg × 1 unit/kg (as FIX recovery after infusion is usually only 50% of the predicted value).

a. Recombinant FVIII or FIX Dose is calculated by above mentioned formula. Half life of FVIII is 8-12 hours so given twice daily, whereas FIX half life being 24 hours given once a day. Other FVIII preparations used in haemophilia A are (i) Fresh frozen plasma FFP. (ii) Cryoprecipitate. They are indicated in major bleeds, surgery or dental extractions.

Table 20: Severity of haemophilia A.

Severity	*FVIII activity of normal*	*Age of presentation*	*Clinical effect*	*Haemarthrosis*
• Mild	6-30%	Young adults	Severe trauma or surgery	Rare
• Moderate	1-5%	Children 1-5 years	Bleeding on slight injury	Uncommon
• Severe	<1%	At birth	Spontaneous bleeding episodes often	Frequent
Factor replacement in haemophilia				
Units = % rise in factor required body wt. (kg)				
Factor IX deficiency, K = 1				
Factor VIII deficiency, K = 2				

b. Desmopressin (DDAVP) – 0.3 µg/kg iv combined with an antifibrinolytic agent increases factor VIII levels in haemophilia A, and may be used to avoid treatment with blood products. It's not useful in severe cases as there is no storage for release. Antifibrinolytic agents have been combined with factor concentrates when bleeding is external (e.g. in dental extraction) but have not usually been used with factor IX concentrates (because of the risk of thrombosis) or in haematuria (because of the risk of clot retention).

Prophylactic treatment – is useful in selected patients. Factor VIII inhibitors develop in 10-25% of haemophilia A sufferers, and it is likely that high-purity concentrates are more likely to promote inhibitor development. Factor IX inhibitors are uncommon in haemophilia B.

Genetic counselling is important in families affected by haemophilia. Direct defect analysis using DNA technology is now being used in antenatal diagnosis.

VON WILLEBRAND'S DISEASE

Von Willebrand's disease is an autosomally inherited bleeding disorder caused by a qualitative or quantitative defect in on Willebrand factor (vWF). Both sexes are affected. The disease may be classified into 3 main types:

- *Type 1* – Partial quantitative deficiency of vWF (autosomal dominant, 70% of cases)
- *Type 2* – Qualitative deficiency of vWF (autosomal dominant/recessive, 25%)
- *Type 3* – Almost complete absence of vWF (autosomal recessive, 5%).

Acquired VWD is a rare disorder, most commonly seen in patients with underlying lymphoproliferative disorders, including monoclonal gammopathies of undetermined significance (MGUS), multiple myelom and Waldenström's macroglobulinemia.

Clinical features – Milder forms may present in second or third decade; clinically significant disease usually presents earlier. Mucosal bleeding (particularly epistaxis) and bleeding after injury or surgery are the main symptoms. Joint and muscle bleeds are rare.

Lab. investigations– (a) Prolonged bleeding time because of defect on platelet formation. (b) APTT slightly prolonged. (c) Ristocetin-induced aggregation defective (diagnostic of vWD). (d) Platelet count normal.

Management – (a) DDAVP combined with an antifibrinolytic agent is sufficient for haemostatic control in most patients; blood products should be avoided if possible. (b) Intermediate-purity factor VIII concentrates or specific vWF concentrates are used when DDAVP is contraindicated. (c) Cryoprecipitate.

ACQUIRED DISORDERS OF COAGULATION

1. *Vitamin K deficiency*
   - Anticoagulant drugs - Coumarins, heparin
   - Biliary obstruction
   - Vitamin K malabsorption
   - Haemorrhagic disease of newborn
2. *Disseminated intravascular coagulation*
3. Others:
   - Massive blood transfusion due to deficiency of labile haemostatic factors particularly V and VII and platelets
   - Liver disease
   - Multiple myeloma

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

DIC is a syndrome in which either the extrinsic or intrinsic factor or both are activated resulting in multiple fibrin clots in small blood vessels. Causes of DIC are enumerated in Table 21.

Clinical features of acute DIC are listed in Table 22.

Laboratory Diagnosis

Acute DIC – (a) FDP levels assayed as the plasma digestion product of factor XIII cross-linked fibrin (D-dimer) may be increased by secondary fibrinolysis. (b) PT may be prolonged. (c) Prolonged APTT. (d) Reduced platelet count (e) Presence of schistocytes on blood smear (f) Fibrinogen levels reduced only in severe cases (g) Antithrombin III or plasminogen activity <60% of normal.

Chronic DIC – (a) FDP and D-dimer levels elevted. (b) Within normal range to high clotting time, PT or APTT (c) Normal or raised concentration of circulating fibrinogen. (d) Reduced number of platelets. (d) Short clot lysis time, evidence of fibrinolysis. (e) Fragmentation of red cells may occur in presence of kidney or malignant disease but less copmpared to acute DIC.

Management

1. **General measures**– (a) Correction of primary condition. (b) Restoration of fluid balance. (c) Treatment of shock, acidosis and hypoxia.

Table 21: Causes of DIC.

Acute DIC
1. Obstetric complications
• Amniotic fluid embolism
• Eclampsia
• Premature separation of placenta
• Retained dead foetus/placenta
2. Malignancies
• Acute promyelocytic leukaemia
• Adenocarcinoma (metastatic mucus secreting)
3. Infections
• Septic abortion
• Gram negative sepsis
• Clostridium welchii septicaemia
• Meningococcal septicaemia
• Falciparum malaria
4. Miscellaneous
• Severe burns
• Heat stroke
• Snake bite
• Anaphylaxis
• Severe trauma
• Post surgery
• PNH
• Fat embolism
Chronic DIC
1. Malignancies
• Leukaemia
• Solid tumours
2. Obstetrics
• Retained products of conception/dead foetus
3. Hematologic
• Myeloproliferative neoplasms
• PNH
4. Inflammatory
• Ulcerative colitis
• Crohn's disease
• Sarcoidosis

Table 22: Clinical features of acute DIC.

Bleeding
• Spontaneous bruising
• Petechiae
• Prolonged bleeding from venepuncture sites, arterial lines, etc.
• Bleeding into GI tract or lungs
• Secondary bleeding after surgery
• Coma (intracerebral bleeding)
Clotting
• Acute kidney failure (ischemia of renal cortex)
• Venous thromboembolism
• Skin necrosis or gangrene
• Liver failure (due to infection and hypotension)
• Coma (cerebral infarction)
Shock: due to underlying disease together with DIC.
Central nervous system
• Transient neurological symptoms and signs
• Coma
• Delirium
Lungs
• Transient hypoxemia
• Respiratory haemorrhage
• Adult respiratory distress syndrome

2. **Specific therapy**– (a) *Heparin* – indicated in deep vein thrombosis of lower limb, pulmonary embolism or peripheral gangrene. *Dose* – 15,000-25,000 units/24 hours. (b) *Replacement of coagulant factors* – Platelets or fresh whole blood is required when haemorrhagic state is increasing despite general and specific measures. Fresh frozen plasma (FFP) and platelet concentrates (at a dose of 1 -2 U/10 kg body weight in marked thrombocytopenia) are satisfactory fractions. Low levels of fibrinogen (<100 mg/dL) or brisk hyperfibrinolysis will require infusion of cryoprecipitate. The replacement of 10 U of cryoprecipitate for every 2-3 U of FFP is sufficient to correct the hemostasis. (c) *Inhibition of excess fibrinolysis.*

OTHER ANTICOAGULATION DISORDERS

Haemorrhagic disease of the newborn

Vitamin K deficiency in the neonate due to defective synthesis of vitamin K from delayed colonization of the gut:

- Bleeding from umbilical cord stump or melena 2-3 days after birth. Intracranial bleeding or intramuscular hemorrhage may occur.
- Prolonged PT and APTT.
- Vitamin K given parenterally produces quick response.

Liver disease

- Deficiency of factors synthesised in the liver (II, VII, IX, X). Low levels of FV and fibrinogen, if severe liver disease.
- PT, APTT prolonged.
- GI hemorrhage from gastritis or peptic ulcer common.

Table 23: Severity of hemorrhage and platelet count.

Platelet count (10^9/litre)	*Clinical effect*
• > 500	• Hemorrhage or thrombosis
• 100-500	• No clinical effect
• 50-100	• Moderate hemorrhage after injury
• 20-50	• Purpura may occur
	• Hemorrhage after injury
• < 20	• Purpura common • Spontaneous bleeding from mucous membranes • Intracranial hemorrhage (rare)

PLATELET DISORDERS

Normal platelet count is 150-450 × 10^9/litre, regardless of age. The severity of hemorrhage is directly related to platelet count (Table 23).

Thrombocytopenia is the condition in which platelet count falls below 100 × 10^9/L. Causes of thrombocytopenia are listed in Table 24.

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

It is characterized by Immune Mediated Destruction

Clinical features:

Acute thrombocytopenia – If severe and of sudden onset, may cause widespread purpura, bruising, mucosal bleeding, cerebral and GI haemorrhage. Fundal haemorrhage, persistent headache and other signs of increasing intracranial pressure suggest intracranial bleeding. Children with acute thrombocytopenia are at less risk than adults. When the condition develops after viral infection, e.g. measles, EBV infection, the duration is brief, active treatment is not required and recovery is nearly always complete.

Chronic ITP – is most common in young adults, especially women. Most patients have purpura, epistaxis, and often menorrhagia. Symptoms tend to fluctuate, with fairly long remissions as well as periods when symptoms increase spontaneously. Commonly occur after a viral infection.

Table 25 compares features of acute ITP and chronic ITP.

Severity of bleeding in ITP is determined by platelet count (Table 26).

Investigations

1. *Blood*
   Thrombocytopenia
   Hb decreased

Table 24: Causes of thrombocytopenia.

1. Decreased platelet production	
Hypoplasia of megakaryocytes	
• Chlorthiazide, ethanol	
• Amegakaryocytic thrombocytopenia	
2. Increased platelet destruction	
a. Idiopathic	
Immune thrombocytopenia	
b. Secondary	
(i) *Immune mechanisms*	
• Collagen vascular disease	
• Lymphoproliferative disorders	
• SLE	
• Drug-induced	
Diclofenac	Isoniazid
Digoxin	Quinine
Tamoxifen	Gold salts
Heparin	Glibenclamide
(ii) *Non-immune mechanisms*	
• DIC	• Acute leukaemia
• TIP	• Myelosuppressive drugs
• Aplastic anaemia	• Cyclophosphamide, busulphan, etc.
3. Abnormal pooling of platelets	
• Splenomegaly, congestive, neoplastic	
4. Other causes	
• Hepatitis	
• Malignancy	
• Pregnancy	
• HIV infection	
• Infectious mononucleosis	
• Parvovirus	

   Antiplatelet antibodies
2. *Bone marrow*
   - Megacaryocytic hyperplasia
   - Non-functioning megacaryocytes. Absence of budding of platelets from cytoplasm
   - Erythroid hyperplasia due to anaemia
   - Iron stores diminished, if severe bleeding is one of the features

Management of chronic ITP:

1. ***Conservative treatment***
   a. *Bleeding not severe* – Wait and see policy especially in children and young women upto the age of 25, because spontaneous remission, often permanent occurs in number of patients. Initiate treatment when PCT <30,000.

Table 25: Features of acute ITP and chronic ITP.

	Acute ITP	*Chronic ITP*
• Age	• Children 2-8 yrs	• Adults 20-45 yrs
• Sex	• Equal	• M : F 1-3
• History of preceding viral infection	• In most pts.	• —
• Onset	• Sudden	• Insidious
• Duration	• 2-8 weeks	• Months to yrs
• Spontaneous remission	In majority	Rare
• Platelet count	• < 20×10^9/L	• 30-60 × 10^9/L

b. *Severe bleeding* – (i) Blood transfusion. (ii) Prednisolone – 40 mg a day for 2 weeks. Sometimes permanent remission. Observe patient at intervals for next 12 months. If purpura disappears partially or completely but platelet count remains low, 5-15 mg. of prednisolone daily for a further period of at least 3 months in the hope that permanent remission will occur.

2. ***Immunosuppressive therapy*** – Drugs such as azathioprine or cyclophosphamide are sometimes used in patients who are refractory to splenectomy and steroids or develop relapse.
3. ***Immunoglobulin preparations*** – IV infusions of large doses result in reticuloendothelial blockade, and may be warranted in life-threatening situation.
4. ***Rituximab*** weekly in doses of 375 mg/m^2 can produce remission for a period of time.
5. TPO receptor agonists – Romiplostim (given subcutaneously) and another orally eltrombopag (given orally) effective in raising platelet counts in patients with ITP and are recommended for adu lts at risk of bleeding who relapse after splenectomy or who have been unresponsive to at least one other therapy, particularly in those who have a contraindication to splenectomy.
6. Splenectomy – *Indications* – (a) Chronic cases, particularly adults, who have not had sustained response to steroids, and in whom troublesome bleeding persists after 6 months. (b) Symptoms severe and platelet count very low. (c) Signs of incipient central nervous system haemorrhage. (d) Girls approaching age of onset of menstruation. (e) Young married women likely to become pregnant. (f) First 5 months of pregnancy. (g) Steroid refractory.

Table 26: Platelet count and severity of bleeding in ITP.

Platelet count (×10^9/L)	*Severity of bleeding*
> 50	No spontaneous bleed
10-50	Bleeding in skin and mucus membranes
< 10	Post-traumatic bleeding, serious GI, and genitourinary bleeding

VASCULAR DISORDERS

Intact vascular endothelial function and the ability of vessels to contract are essential components by which blood loss is controlled. Abnormal vessel walls can result in excessive bleeding which is usually bleeding into the skin (petechiae or bruising) or mucous membrane (nose bleeds or GI blood loss). Routine laboratory screening tests for haemostasis are normal.

Causes

A. *Hereditary*

1. **Hereditary haemorrhagic telangiectasis** (HHT) is inherited as autosomal dominant, a gene causing HHT has been identified. HHT is characterised by structural abnormalities of blood vessels resulting in telangiectases– thin-walled, dilated, convoluted tubules connecting directly to dilated arteries that bleed easily. The skin, nose and GI tract may be affected, and bleeding may be mild or sufficiently severe to require multiple blood transfusions. A-V malformations comprising direct connections between a branch of an artery and a vein are seen in a minority of patients; these may be found in the lung (causing cyanosis or polycythemia) and in the brain (causing stroke or leading to brain abscess).

   Diagnosis – is based on family history and presence of telangiectases or at endoscopy.

   Management – Local measures to control bleeding and correction of anaemia with iron. Regular transfusion may be required. Genetic counselling should be offered.
2. **Ehlers-Danlos syndrome** is a disorder of collagen with a variable inheritance pattern. Patients have hyperflexible joints and elastic skin, and bleed abnormally following injury.
3. **Marfan syndrome.**
4. **Thrombopoietic agonists** like Romaplastin.

B. *Acquired:*

- **Scurvy** – Vitamin C deficiency causes an acquired abnormality of collagen leading to bleeding gums, and perifollicular and subperiosteal hemorrhage. Administration of vitamin C produces rapid improvement.

- **Henoch-Schonlein purpura** – is an immune - complex mediated hypersensitivity reaction leading to vasculitis. It occurs most commonly in children after acute infection. Patients present with purpura (typically affecting the buttocks and extensor surfaces, of the legs), but the condition is usually self-limiting.
- **Corticosteroid-induced purpura** – may occur in patients receiving long-term corticosteroid therapy and in Cushing's syndrome.
- **Senile purpura** – results from atrophy of the tissues that support cutaneous blood vessels.
- **Purpura associated with infection** – Bacteria, viruses and Rickettsia may cause purpura by direct vascular damage or as a result of immune complex formation. Overwhelming infection (particularly meningococcal septicaemia) is often associated with purpura, thrombocytopenia and DIC.
- **Simple easy bruising** is common particularly in young women.
- **Fat embolism.**

8. ANTICOAGULANT DRUGS

Anticoagulation prevents pathological clot formation (e.g. on heart valves or atria) and stops prolongation and embolization of clots already developed in veins. The type, intensity and duration of anticoagulation depends on the indication for treatment (Table 27).

ANTICOAGULANT DRUG THERAPY

Tests to perform– Before starting warfarin or heparin a clotting screen (prothrombin time, partial thromboplastin time and thrombin time) and platelet count are performed. LFTs should be checked before starting warfarin. Serious kidney dysfunction should be excluded before starting low molecular weight heparin.

Table 27: Indications for anticoagulation.

Prophylaxis of deep venous thrombosis
Treatment of deep venous thrombosis/pulmonary embolism
Atrial fibrillation
Dilated cardiomyopathy
Mural thrombus post-myocardial infarction
Rheumatic mitral valve disease
Atrial fibrillation for cardioversion
Recurrent deep vein thrombosis/pulmonary embolism (in patients on warfarin)
Mechanical heart valves

Heparin

Unfractionated heparin is extracted from porcine mucosa. It is a heterogenous mixture of polysaccharide chains of molecular weight 3-30 kDa.

Low molecular weight heparins are produced by depolymerisation, yielding chains of 4-6 kDa. Both forms can bind and activate antithrombin (AT), accelerating the interaction of AT with activated factor X (Xa) by 1000 fold.

Difference between unfractionated and LMWH:

1. LMWH has an anti-Xa activity of >90%, unfractionated heparin has < 30% at prophylactic doses.
2. LMWHs after s.c. injections are better absorbed and have a greater bioavailability.
3. The half-life of s.c. LMWHs (3-6 hrs) is 2-4 times that of unfractionated heparin. Urinary excretion of LMWH is reduced by kidney impairment.
4. LMWH has a lower affinity for platelet factor and therefore a lower incidence of HITT.

Dosage and administration

Therapeutic doses of heparin vary from molecules used (Table 28) and require daily monitoring (APTT 1.5-2.5 times control); prophylactic doses are determined by thrombotic risk and do not require laboratory testing. Monitoring of LMWH is necessary only in kidney failure and pregnancy.

Complications

1. **Bleeding** – is not directly related to heparin dose, though the risk is low at prophylactic doses and is increased by concurrent illness, age and aspirin use. Risk is less with LMWH. Protamine 1 mg/100 units, reverses the action of unfractionated heparins, less effective against LMWH.
2. **Thrombocytopenia** – is caused by both types of heparin. A fall in platelet count is occasionally seen soon after starting heparin; it has neither haemorrhagic nor thrombotic consequences.

   Heparin - induced thrombocytopenia with thrombosis (HITT) can lead to venous and arterial gangrene. This reaction is mediated by an IgG antibody against complexes of heparin and platelet factor 4. It usually develops after 5 or more days therapy, but can appear sooner in patients exposed to heparin (usually unfractionated) and causes platelet activation.
3. **Osteoporosis** – can develop after several months heparin treatment.

Warfarin

Warfarin (a coumarin) is the standard oral anticoagulant, Vitamin K-dependent factors II, VII, IX and X and coagula-

Table 28: Heparin treatment regimens.

Drug	*Indication*	*Recommended Regimen (Once - Daily Subcutaneous Injection*
Dalteparin	• Prophylaxis – moderate risk	2500 units[1]
	• Prophylaxis – high risk	5000 units
	• Treatment of deep vein thrombosis/pulmonary embolism	200 units/kg
	• Treatment of unstable coronary disease	120 units/kg 12-hourly
Fondaparinux	• Risk of HITT lower than with LMWH	2.5 mg od
Enoxaparin	• Prophylaxis – moderate risk	20 mg (2000 units)
	• Prophylaxis – high risk	40 mg (4000 units)
	• Treatment of deep vein thrombosis/ pulmonary embolism	1 mg (100 units)/kg 12-hourly
	• Treatment of unstable coronary disease	1 mg (100 units)/kg 12-hourly
Tinzaparin	• Prophylaxis – moderate risk	3500 units
	• Prophylaxis – high risk	50 units/kg
	• Treatment of deep vein thrombosis/ pulmonary embolism	175 units/kg
Reviparin	• Prophylaxis – moderate risk	1432 U bd
	• Prophylaxis – high risk	3436 U bd
Nadroparin	• Prophylaxis – moderate risk	3075 U bd
	• Prophylaxis – high risk	6150 U bd
Certoparin	• Prophylaxis – moderate risk	3000 units
	• Prophylaxis – high risk	3000 units
Unfractionated heparin (sodium or calcium)	• Prophylaxis – moderate risk	5000 units 12-hourly
	• Prophylaxis – high risk	5000 units 8-hourly
	• Treatment of deep vein thrombosis/ pulmonary embolism	5000 units i.v. followed by 1000-2000 units/ hour i.v. infusion monitored by activated partial thromboplastin time

Moderate risk – general surgery, age > 40 years, no additional risk factors.

High-risk – major orthopaedic surgery, major general or gynaecological surgery with additional risk factors (malignancy, history of venous thromboembolism, varicose veins, obesity, immobility, sepsis, thrombophilia).

tion inhibitors proteins C and S require carboxylation to form functional complexes; warfarin inhibits this process.

Warfarin is absorbed rapidly. Plasma peak levels are achieved in about 1.5 hours and t½ is 2-3 days. Onset of action depends on the levels of factors II, VII, IX and X.

Dosage and monitoring

The dose is usually 3-9 mg/day, but can range from 0.5 mg/day to 25 mg/day. The dose is adjusted from day 2, on the basis of 'international normalised ratio' (INR), usually > 2-2.5 on 2 consecutive days.

High doses of warfarin can result in rapid reduction of the anticoagulant proteins C and S, and can result in thrombosis of subcutaneous vessels and skin necrosis. To prevent this, heparin is given before starting warfarin in all patients with venous thrombosis, or a history or family history of venous thromboembolic disease, it should be continued until INR is > 2 for 2 days. In patients requiring anticoagulation for indications other than thrombosis (e.g. atrial fibrillation), a history of venous thrombosis should be excluded before starting warfarin, and the starting dose should not exceed 5 mg daily.

Problems during Warfarin Therapy

1. **Drug interactions** – Many drugs interact with warfarin (e.g. amiodarone) and certain antibacterials (particularly ciprofloxacin, erythromycin and metronidazole) increase INR. NSAIDs and antiplatelet agents (dipyridamole, aspirin and clopidogrel) increase GI tract bleeding. Corticosteroids, thyroxine, allopurinol, omeprazole and lipid-regulating drugs enhance action of warfarin. Paracetamol (> 28 tablets / per week) can increase INR. Antiepileptics, rifampicin and griseofulvin usually antagonize warfarin.

Other factors affecting warfarin requirements – include CHF, liver impairment, variations in alcohol intake, marked variations in diet, vomiting and diarrhoea.

Recommendations for high NIR (without bleeding):

- INR > target range with no bleeding – Omit warfarin for 1-2 days, recommence at lower dose
- INR > 8.0 with no bleeding – Omit warfarin until NIR < 5%, give vitamin K 0.5-2.5 mg p.o., if there are risk factors for bleeding.

2. **Bleeding**– Risk of bleeding rises with INR > 5, but serious (e.g. intracranial) hemorrhage can occur even at target INR. Major bleeding, irrespective of INR, requires prothrombin complex concentrate, 50 units/kg, or fresh frozen plasma, 15 mg/kg. Vitamin K can be given p.o. or slow iv. Minor bleeding (e.g. epistaxis, bruising, subconjunctival hemorrhage) should be assessed and warfarin reduced or withheld as necessary. Local measures to stop bleeding may be necessary.
3. **Surgery** – Patients taking warfarin should not undergo surgery unless INR has been adjusted beforehand.

Acenocoumarol

Dosage – Initial 8-16 mg to maintain prothrombin time 2-3 times control value. It generally takes 7-10 days to stabilize the patient on a regular dosage. As compared to Warfarin, the drug has better anticoagulant stability and INR value within the therapeutic range over a significantly longer duration of treatment period.

Dabigatran Etexilate

Superior to warfarin preventing systemic embolism with reduced risk of bleeding. **It inhibits thrombin action**. Dose - 150 mg b.d. Dose not require anticoagulant monitoring.

Precaution: Kidney function to be ascertained on an ongoing basis, if it declines, e.g. hypovolemia, dehydration or with certain comedications. *Contraindications* - Severe renal impairment, patient with a bleeding diathesis or patients with spontaneous or pharmacological impairment of haemostasis.

Rivoraxban and Apixaban- newer oral anticoagulant. It inhibits action of factor Xa. Used for thromboprophylaxis in cases of elective knee or hip arthroplasty.

9. MYELODYSPLASTIC SYNDROMES

CLASSIFICATION OF MDS

The myelodysplastic syndromes (MDS) constitute a heterogenous group of malignant bone marrow disorders characterised by ineffective haemopoiesis and increased risk of leukemic evolution (Table 29).

Pathogenesis

MDS is a clonal disorder of an early haemopoietic progene or stem cell. Increased apoptosis in the progenitor is a hall mark of MDS. No single genetic lesions has been shown to be sufficient for developing the disease.

Clinical Features

Generalised weakness, easy fatiguability anemic features predominate early in course. Children with Down syndrome are susceptible to MDS and a family history may indicate a hereditary form of sideroblastic anemia, Fanconi anemia or a telomeropathy.

Treatment

1. *Transfusion* - (a) RBC transfusion to avoid significant anaemia. (b) Platelet transfusion if significant thrombocytopenia.
2. *Iron chelation* - Desferrioxamine s.c. or IV infusion, or oral iron chelators like deferiprone or deferasiorx.
3. *Erythropoietic growth factors* - EPO s.c. inj. 1-3 times/wk, in a weekly dose of 30,000 to 60,000 units. Patients with refractory anaemia and ringed sideroblasts respond better to EPO and G-CSF combination then EPO alone.
4. *Lenalidomide.* 10 mg/days for 21 days on and one week off. Indicated in low risk and intermediate risk MDS patients.
5. *Hypomethylating agent* is recommended as first line therapy in patients with high risk MDS, therefore not eligible. Decitabine which is an alternate to 5-AZA cytidine allogenic stem cell transplantation. 5-AZA cytidine 75 mg s.c. or IV daily for 7 days, the cycle to be repeated every 4 weeks with minimum of 4 cycles.
6. Immunosuppression- also may produce sustained independence from transfusion and improve survival. ATG, cyclosporine and the anti-CD52 monoclonal antibody alemtuzumab are especially effective in younger MDS patients.
7. *Allogen stem cell transplantation.* Disease recurrence and nonrelapse mortality are major causes of treatment failure.

Chronic Myeloproliferative Disorders

Classification of CMPD (WHO): Based on cell line, which is predominating hyperplastic.

- Chronic myeloid leukaemia bcr-abl chromosome positive
- Chronic neutrophilic leukaemia
- Chronic eosinophilic leukaemia, not otherwise specified
- Primary myelofibrosis

Table 29: Classification of MDS (WHO).

Disease	*Peripheral blood picture*	*Bone marrow features*
1. Refractory cytopenias with unilineage dysplasia (RCUD)		
a. Refractory anaemia (RA)	• Anaemia	Erythroid dysplasia with <5% blasts
	• Rare blast <1%	
b. Refractory neutropenia (RN)	Neutropenia; blast <1%	Granulocytic dysplasia with <5% blasts
c. Refractory thrombocytopenia	Thrombocytopenia; blast <1%	Megakaryocytic dysplasia with <5% blasts
2. Refractory anaemia with ring sideroblasts (RARS)	• Anaemia; no blast	• Erythroid hyperplasia with dyserythropoiesis
		• < 15% ring sideroblasts, <5% blasts.
3. Refractory cytopenia with multilineage dysplasia (RCMD)	• Bi/pancytopenia • Rare blasts <1%	Dysplasia of ≥2 of the 3 haemopoietic cell lines ± ringed sideroblast
		< 5% blasts.
	No Auer rods	**No Auer rods**
4. Refractory anaemia with excess blasts-1 (RAEB-1)	• < 5% blasts	5-9% blasts
	• Bi/pancytopenia	Dysplastic changes in ≥1% haemopoietic cell line.
5. Refractory anaemia with excess blasts-2 (RAEB-2)	• 5-19% blasts	10-19% blasts.
	• Cytopenias	Myelodysplasia of ≥ 1 cell line.
	± Auer rods	**±Auer rods**
6. MDS unclassified (MDS-U)	• No blasts.	< 5% blasts
	• Cytopenias	Granulocytic or megakaryocytic dysplasia
		If no dysplasia, MDS-associated karyotype
7. MDS with isolated del (5q)	• < 1% blasts	Isolated 5q31 deletion < 5% blasts
	• Anaemia	↑/N megakaryocytes with hypolobated nuclei
	• Platelets/N	
8. Childhood MDS including refractory	Pancytopenia	<5% blast and hypocellular marrow cytopenia of childhood (provisional) (RCC)

- Polycythemia vera
- Essential thrombocythemia
- Myeloproliferative disorder - unclassifiable
- Mastocytosis

POLYCYTHEMIA VERA

Polycythemia vera is one group of polycythemic states that are defined by raised haematocrit (> 0.51 in men, > 0.48 in women), in which phenotypically normal red cells, granulocytes and platelets accumulate in the absence of a recognizable physiologic stimulus.

Etiology

The etiology of PV is unknown. Chromosome abnormalities such as deletion 20q and trisomy 8 and 9 have been documented in up to 30% of PV patients. However, a mutation in the autoinhibitory pseudokinase domain of the tyrosine kinase JAK2, causing constitutive kinase activation appears to have a central role in the pathogenesis of PV.

Vascular complications are the most common presenting feature, and may be arterial particularly cerebral thrombosis and including digital microvascular occlusion, or venous. Increased viscosity caused by raised haematocrit and increased number of platelets (often abnormal in function) contribute to the vascular occlusive tendency. There is paradoxical increased risk of hemorrhage. Due to the large turnover of hematopoietic ce1ls, hyperuricemia with secondary gout, uric acid stones.

Table 30 gives diagnostic criteria of polycythemia vera.

Investigations

Exclusion of causes of secondary erythrocytosis
Hypoxemia (with activation of normal erythropoietic mechanism).

- Chronic lung disease
- Cyanotic congenital heart disease
- Sleep apnoea
- High oxygen affinity haemoglobins

Table 30: Diagnostic criteria of polycythemia vera.

Major criteria		*Minor criteria*	
A1	Raised RBC mass	B1	Thrombocytosis (platelet count > 400 × 10^9/litre)
A2	Absence of cause of secondary erythrocytosis	B2	Neurtophil leucocytosis (neutrophil count > 10 × 10^9/L)
A3	Palpable spleno megaly	B3	Splenomegaly demonstrated on isotope scanning/ ultrasonography
A4	Clonality marker (acquired abnormal marrow karyotype)	B4	Characteristic growth of burst-forming units, erythroid or reduced serum erythropoietin

Polycythemia vera is established by presence of A1 and A2 plus A3 or A4 or any two B.

Renal (with inappropriate secretion of erythropoietin)

- Hypernephroma
- Polycystic kidneys
- Postrenal transplantation

Miscellaneous (ectopic and/or inappropriate secretion of erythropoietin)

- Hepatoma and liver disease
- Cerebellar haemangioblastoma
- Familial autonomous high erythropoietin production

Further investigations may be necessary to fulfil the criteria shown.

1. *An abnormal acquired karyotype* is regarded as evidence of clonal evolution and is a major diagnostic criterion in polycythemia vera. No single karyotypic abnormality is common to all patients; trisomies of 1, 8, 9 and deletions of 13q and 20q are among the more common.
2. *Palpable splenomegaly* in presence of absolute erythrocytosis and no cause for secondary erythrocytosis is also a major diagnostic criterion.
3. *Bone marrow* – Hypercellularity with multilineage hyperplasia and large megakaryocytes with hyperlobulated nuclei are the classical features (Fig. 28).
4. *Raised serum uric acid*
5. *Decreased erythropoietin levels*
6. *Transcobalamin I and III* increased suggesting increased granulocyte turnover.
7. JAK-2 mutation

Differential Diagnosis

Relative erythrocytosis is characterised by normal RCM, but raised PCV. It is often associated with obesity, alcohol, smoking and hypertension.

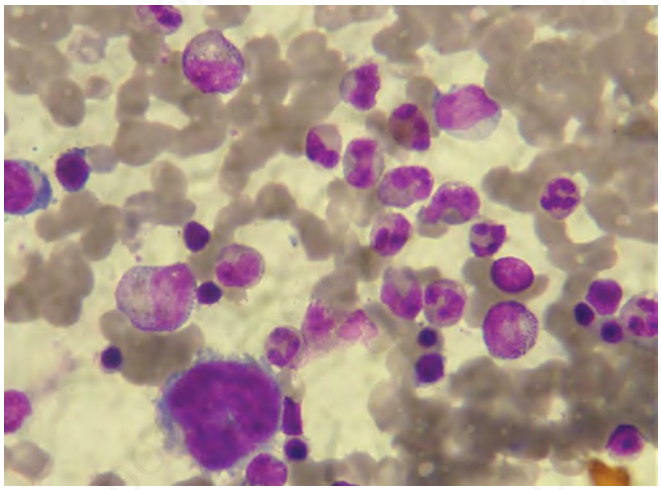


Fig. 28: Polycythemia vera—bone marrow showing trilineage proliferation

Idiopathic erythrocytosis is diagnosed in patients with raised RCM but no identified cause of secondary erythrocytosis and insufficient diagnostic criteria for polycythemia vera. This is a heterogenous group that may include early or unrecognised stages of polycythemia vera or secondary erythrocytosis, and some rare causes of erythrocytosis (e.g. truncation of erythropoietin receptor).

Management

1. *Venesection* – repeated every 2-3 months to maintain the hemoglobin level at <14 g/dL and hematocrit <45% in men and 12 g/dL and hematocrit <42% in women is mandatory to avoid thrombotic complications.
2. *Cytotoxic therapy* – Hydroxyurea 0.5-1.5 mg/day, reduces need for venesection and controls platelet count. Earlier therapies with radioactive 32-phosphorus injections (which suppressed all haemopoiesis) and intermittent low dose busulphan (which controlled mainly the platelet count), now tend to be reserved for the elderly.
3. *Low-dose aspirin* – is particularly useful in patients with micro-vascular occlusion.
4. *Anagrelide* a phosphodiesterase inhibitor is preferable to hydroxyurea urea because if lacks marrow toxicity.
5. *Interferon-α* reduces JAK_2 (defected by PCR) expression in PV patients and can control the disease.
6. Nonspecific JAK2 inhibitor ruxolitinib- undergoing clinical trials in PV patients intolerant to hydroxyurea.

Note: Patients with polycythemia vera very occasionally undergo transformation to acute (usually myeloblastic) leukaemia (3-5% at 10 years) with hydroxyurea therapy, more following ^{32}P treatment.

ESSENTIAL THROMBOCYTHEMIA

Persistently raised platelet count (> 600 × 10^9/litre) and abnormal increase in megakaryocytes in bone marrow the principal feature of primary thrombocythemia. Causes of thrombocythemia are listed in Table 31.

Investigations

Blood

- Raised platelet count (>600 × 10^9/L)
- Platelets large and hypogranular (Fig. 29)
- NAP score raised

Bone Marrow

- Megakaryocytic hyperplasia (Fig. 30)
- No evidence of collagen fibrosis

Clinical Features

1. *Asymptomatic* – In about one-half of patients raised platelet count is an incidental finding.
2. *Symptoms due to vascular occlusion,* particularly of small vessels – Cerebral, coronary, splanchnic and deep veins may be affected. Microvascular occlusions present as erythromelalgia (burning pain in extremities) or gangrene of the digits, particularly the toes.
3. *Bleeding* – May occur after minor trauma, particularly in individuals with platelet counts < 1000 × 10^9/litre.
4. *Splenomegaly* – is modest and occurs only in few. In common with other myeloproliferative disorders, patients have a low but definite risk of transformation to acute leukaemia or myelofibrosis.

Management

- *Hydroxyurea* reduces platelet count; reduction to < 400 × 10^9/litre reduces incidence of vascular occlusions. In older patients, and in those with previous thrombotic lesion (or other risk factor for thrombosis), it is used with low dose aspirin.
- Platelet pheresis, if haemostatic problem.
- Anagrelide in patients with recurrent thrombosis.

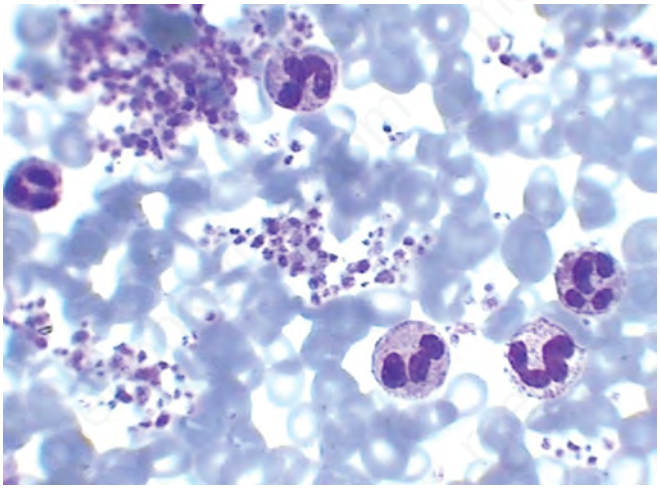


Fig. 29: Peripheral smear showing marked thrombocytosis

Table 31: Causes of thrombocythemia.

I. Primary/Clonal
• Essential thrombocythemia
• Chronic myeloid leukaemia
• Polycythemia vera
• Myelofibrosis
II. Secondary/Reactive
• Infections
• Inflammatory disease
• Malignancies
• Post-hemorrhage
• Post-splenectomy
• Post-surgery
• Miscellaneous - After exercise, parturition, iron deficiency anaemia, hereditary thrombocythemia

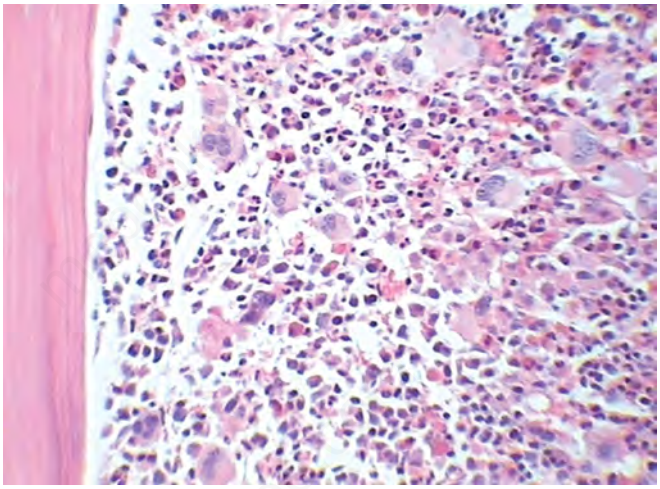


Fig. 30: Essential thrombocythemia—bone marrow biopsy showing megakaryocyte clustering

PRIMARY MYELOFIBROSIS (AGNOGENIC MYELOID METAPLASIA)

In PMF there is marrow fibrosis with extramedullary haemopoiesis in spleen.

Clinical Features

- Weakness or tiredness due to anaemia
- Bleeding episodes due to thrombocytopenia may occur
- Hepatomegaly - Mild due to extramedullary haemopoiesis
- Splenomegaly, moderate to massive. Large areas of extramedullary haemopoiesis in spleen.

Haematological Findings

- Leucoerythroblastic peripheral blood picture (myelocytes and nucleated RBCs) and teardrop cells in peripheral smear
- Elevated Neutrophil alkaline phosphatase score (Normal 40-100)

Bone Marrow

- Dry tap on BM aspiration
- BM trephine biopsy – Increased reticulin fibril network
- Decreased cellularity but increased megakaryocytes
- Dilated marrow sinusoids

Phases of Myelofibrosis

1. Prefibrotic cellular phase with immature and dysplastic megakaryocytes
2. Fibrotic stage
3. Osteomyelosclerosis

Management

Supportive therapy – Transfusion of RBCs, platelets. Treatment of infection. Androgen and recombinant erythropoietin therapy may help in reducing need for transfusions.

Chemotherapy – can be useful, particularly in the proliferative phase of the disease when it can reduce splenomegaly. Hydroxyurea is preferred to alkylating agents, which have a higher leukaemogenic potential.

JAK_2 inhibitors, if JAK_2 mutation is present, useful for reducing splenomegaly and alleviating symptoms.

α-interferon is useful in some cases.

Splenectomy – The risks (bleeding, thromboembolism, infection) must be weighed against the discomfort of splenomegaly, frequent transfusions and thrombocytopenia induced bleeding. Splenic irradiation can be a palliative measure. High-dose corticosteroids can be helpful in severe neutropenia.

Allogenic bone marrow transplantation – should be attempted only in younger patients with poor prognostic features because of the procedure - related morbidity.

Causes of Secondary Myelofibrosis

- Metastatic carcinoma in BM
- Hodgkin's disease with BM involvement
- Chronic myeloid leukaemia
- Hairy cell leukaemia
- SLE
- Post-irradiation
- Leishmaniasis
- HIV infection
- Tuberculosis

10. LEUKEMIAS

A clone of malignant cells derived from myeloid or lymphoid stem cells. In *acute leukaemia* the clones are primitive (blast cells) in type, whereas in *chronic leukaemia* the abnormal cells retain most of the features of their normal counterpart. In children 85% of leukaemias are of lymphocytic type; in adults acute myeloid leukaemia is the most common type.

ACUTE LEUKEMIAS

Acute leukaemias are characterised by an uncontrolled growth of immature haemopoietic cells at the expense of normal marrow tissue. Although acute leukaemia is primarily a disease of the bone marrow, leukemic cells usually circulate in the blood, and may infiltrate other tissues.

Acute leukaemias are divided into two main groups:

- Acute lymphoblastic leukaemia (the blast cells arise from a committed lymphoid cell line)
- Acute myeloid (the precursor cells involved in the malignant process would have normally matured into RBCs, granulocytes or platelets – the cells normally termed 'myeloid').

Table 32 gives WHO classification of leukaemias (Fig. 31).

Aetiology

1. *Unknown* (usually)

Table 32: WHO classification of AML.

• AML not otherwise specified
- Minimally differentiated (M0-5%)
- Without mutation (M1–10%)
- With mutation (M2–30-40%)
- Acute myelomonocytic (M4–15-20%)
- Acute monoblastic and monocytic (M5a, 5b, 5-8%)
- Acute erythroid (M6–5-6%)
- Acute megakaryoblastic (M7-3.5%)
- Acute panmyelosis with myelofibrosis (M7, rare)
- Acute basophilic (very rare)
• Myeloid sarcoma (Chloroma, granulocytic sarcoma, extramedullary masses of monoblasts or myeloblasts)
• AML with recurrent genetic abnormalities
- AML with inv(16) (pI3.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- AMPL variants – t(15:17)(q22;q12); PML-RARA
- AML with t (8:21) (q22;q22); RUNX 1-RUNX1T1
- AML with t(9; 1 1) (p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q 34); OEK-NUP2 7 4
- AML with inv (3) (q 2 1 q26.2) or t(3;3)(q 2 1; q26.2); RPN 7 -EVI 7
- AML (megakaryoblastic) with t(l ;22) (p 1 3;q 1 3); RBM 75-MKL 7
- Provisional entity AML with mutated NPM1
- Provisional entity AML with mutated CEBPA
• AML with myelodysplasia related changes
- MDS or MDS/MPD following or without antecedent MDS
• AML + MDS following therapy related (alkylating agents, topoisomerase inhibitors, other types).
• Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome
• Blastic plasmacytoid dendritic cell neoplasm

2. *Radiation* – Association between radiation-induced genetic damage to the haemopoietic progenitors and the development of myelodysplasia and acute leukaemia is seen after nuclear disasters (e.g. Hiroshima, Nagasaki, Chernobyl). Patients who have received radiotherapy may develop leukaemia.
3. *Chemicals and drugs* – e.g. chronic benzene exposure and use of cytotoxic and immuno-suppressive agents.
4. *Genetic (hereditary) factors* – Genetic disorders like:

Down's syndrome	Klinefelter's syn.
Bloom's syndrome	Osteogenesis imperfecta
Fanconi's anaemia	Wiskott-Aldrich syn.
Ataxia telangiectasia	Leukaemia in siblings

5. *Viruses* – The rare adult T cell leukaemia lymphoma syndrome associated with infection by the human lymphocyte virus I infection.

Clinical Features

Common symptoms and signs at presentation result from leukemic cells, bone marrow failure or organ infiltration.

Onset – Abrupt or insidious, abrupt onset common in children.

1. *Symptoms due* to *anaemia* – Tiredness, weakness, fatigability, marked pallor.
2. *Haemorrhagic manifestations* – Skin petechiae, bruises, bleeding from gums and nose, or persistent bleeding after tooth extraction or tonsillectomy. Gastrointestinal, renal, and bleeding into nervous system may occur. Impairment of vision from haemorrhage in eye or vertigo from haemorrhage in ear.
3. *Infections* – (a) Infective lesions of mouth and throat – Ulceration of mouth and pharynx. (b) Anal, rectal and vaginal ulceration may occur. (c) Herpes simplex infection of face. (d) Infections of respiratory tract such as bronchitis and pneumonia. (e) Of skin namely cellulitis and multiple boils.
4. *Symptoms of cellular hyperviscosity* – due to high counts of circulating blasts (> 10×10^9/litre) – Headache, confusion, fits, focal neurological signs, coma.
5. *Tissue deposits of leukemic cells*, e.g. gum hypertrophy common in myelomonocytic and monocytic varieties of AML (Fig. 32).
6. *Lymphadenopathy and hepatosplenomegaly* – more common in ALL.
7. *Organ infiltration* – (a) *CNS* – Although meningeal involvement is uncommon at presentation, it occurs in 75% of children with ALL. Intracerebral deposits or infiltration of cranial or peripheral nerves. (b) *Skin* – Bluish nodules or dusky red patches. (c) *Kidneys* – leading to kidney failure. (d) *Other sites* – Testes, ovaries, liver, gut particularly stomach, and serous membranes such as pleura and peritoneum.
8. *Bone pains* – common; tenderness of sternum. Osteolytic bone lesions and pathological fractures may occur.
9. *Constitutional symptoms* – Fever, malaise, prostration.
10. *Roth's spots* - White-centered retinal haemorrhages in AML.
11. *Acute haemostatic failure* – In the promyelocytic (M3) variant of AML, release of cytoplasmic granular contents readily activates coagulation and fibrinolytic systems, giving rise to acute haemostatic failure.

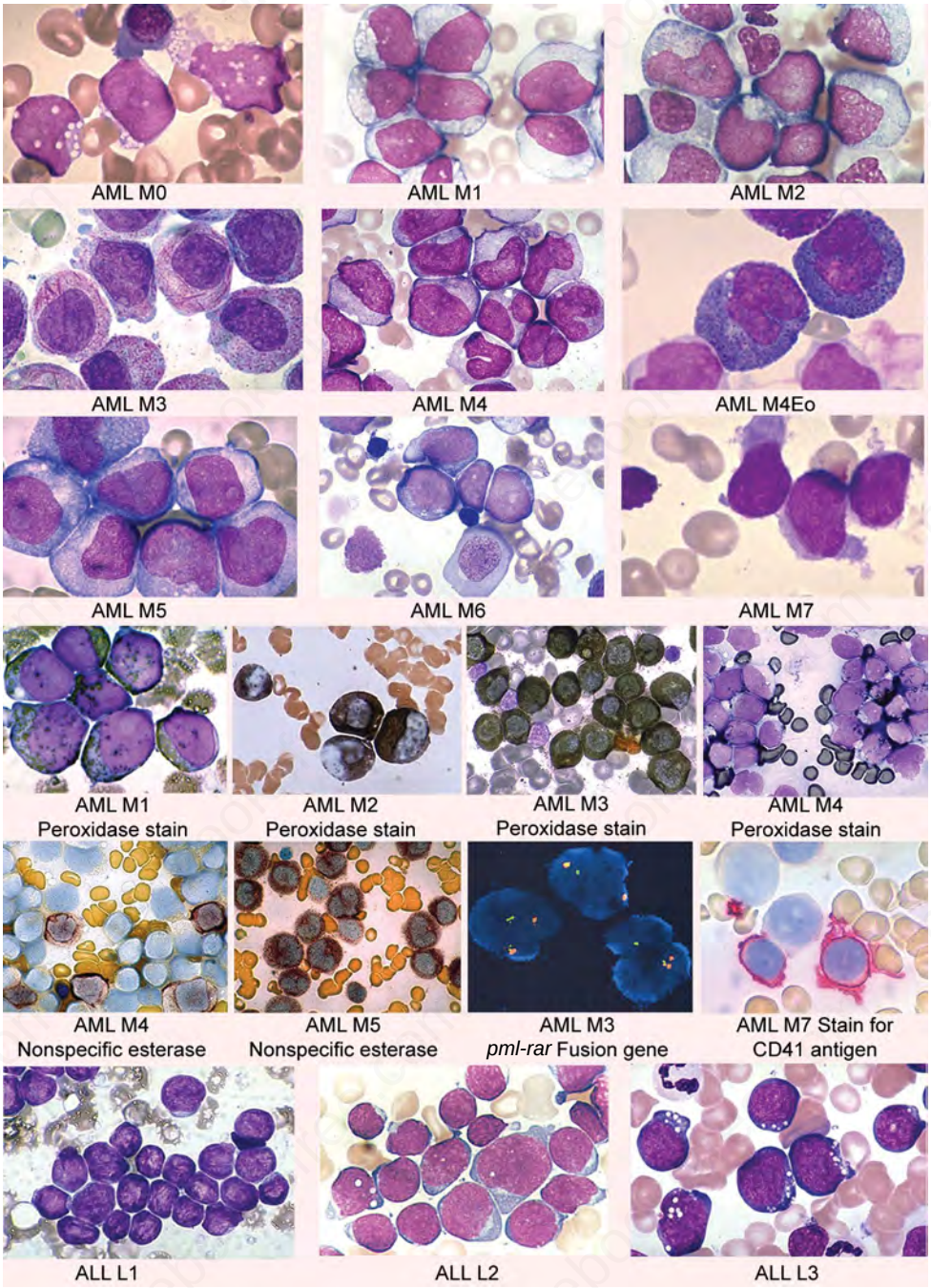


Fig. 31: Acute leukaemia (Myeloid and lymphoid)

12. *Leucostasis* is a fatal complication in granulocytic leukaemia. Some patients with acute myeloid leukaemia have hyperleukocytosis (WBC counts: 1,000,000 mm^3). Leucostasis is a clinicopathological syndrome caused by sludging of circulating leukemic blasts in tissue microvasculature. Leucostasis can affect any organ but symptoms usually arise from involvement of lungs, heart, brain and testes. Clinical presentation in the lung may simulate infection, embolisation and acute respiratory failure.

Table 33 gives differences between ALL and AML.

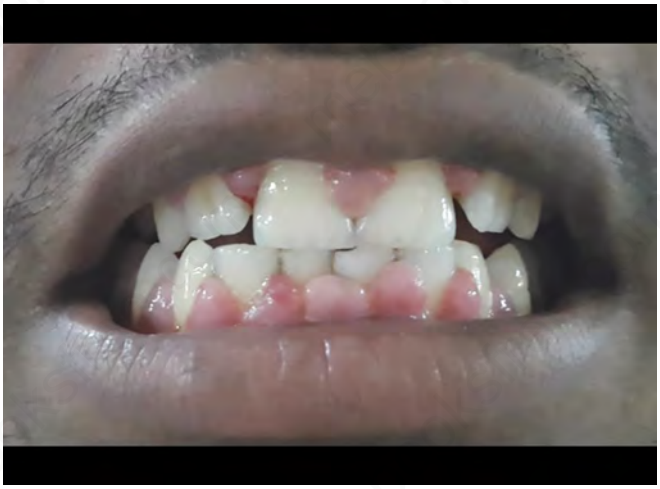


Fig. 32: Gum Hypertrophy

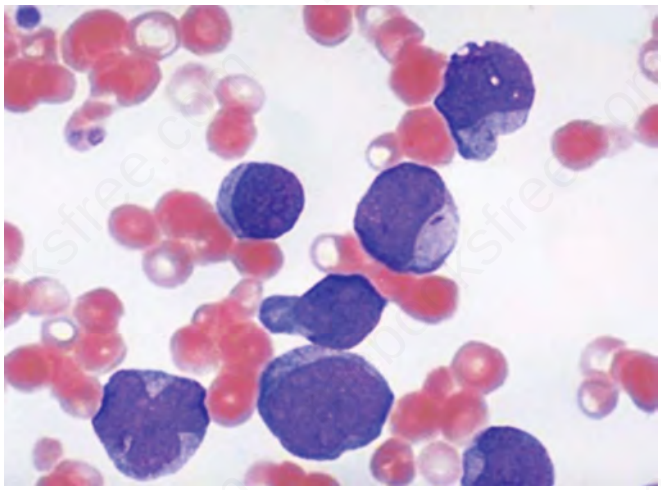


Fig. 33: Acute myeloblastic leukemia (peripheral blood). The myeloblast in the center of the field contains a cytoplasmic auer rod

Investigations

AML – (1) *Total white cell count* – > 500,000/cmm unless aleukaemic leukaemia. (2) *Peripheral blood film* – Increased number of typical or atypical myeloblast; Auer rods may be found in the cytoplasm. (Fig. 33) (3) *Bone marrow aspirate* – More than 30% blast cells. Marrow often entirely replaced by myeloblasts and promyelocytes. Positive Sudan black reaction.

Table 34 gives differences between Lymphoblast and Myeloblast.

ALL

1. *Total white cell count* – More than 50,000 blast cells/cmm (less than 1,000 white cells if aleukaemic leukaemia). (Fig. 34) Can present as neutropenia or pancytopenia.

Table 33: Differentiation between ALL and AML.

Features	*ALL*	*AML*
Age	Common in children	Common in adults
Bleeding at onset	Uncommon	More common
Lymphadenopathy	Common	Usually absent
Hepatosplenomegaly	Mild	Mild
Gum hypertrophy	No	Seen in M4/M5 type
CNS affection	More common	Less common
Skin infiltration	No	Seen in M4/M5
Ocular affection	More common	Less common
Testicular affection	In few	No
Blood findings		
Blast cells	Lymphoblasts smaller than myeloblasts, round or convoluted nucleus	Myeloblasts are larger with multiple nuclei
Auer rods	Not seen	Present in 10-20%
Tdt in blasts	In majority	Rare
Overall prognosis	Good	Bad

Table 34: Differentiation between lymphoblast and myeloblast.

	Lymphoblast	*Myeloblast*
Cell size	Small or moderate	Moderate or large
Nuclear chromatin	Coarse	Fine
Nucleoli	1-2	2-5
Auer rods	–ve	+ve
Accompanying cells	Lymphocytes	Promyelos, myelos, metas and neutrophils
Myelo peroxidase	–ve	+ve
Sudan black B	–ve	+ve
PAS stain	Black positivity	–ve in blasts

2. *Bone marrow* – Hypercellular with depression of normal erythropoiesis, granulopoiesis and thrombopoiesis. As compared to myeloblastic leukaemia the nuclei are round, the cells smaller, the nuclear/cytoplasmic ratio higher, and the number of nucleoli fewer.

Other Investigations

1. *Coagulation screening* – may give abnormal results particularly in promyelocytic leukaemia.
2. *Biochemical screening* – particularly, if leucocyte count is very high, when there may be evidence of renal impairment and hyperuricemia.

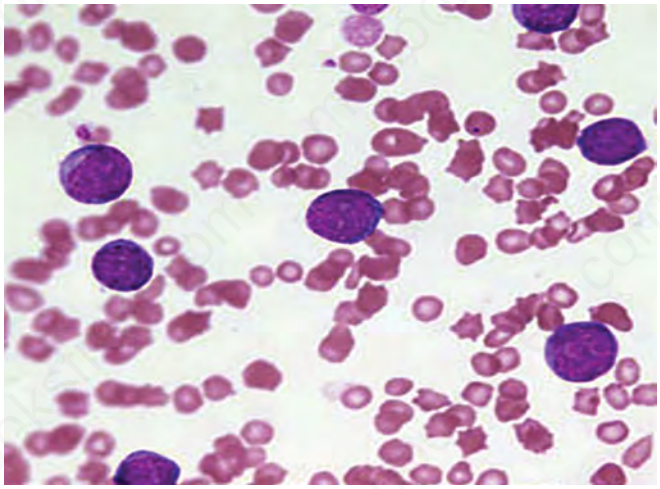


Fig. 34: Acute lymphoblastic leukemia showing numerous lymphoblasts

3. *Chest radiograph* – to exclude presence of mediastinal mass (present in upto 70% of patients with T cell ALL). In childhood acute ALL, lytic bone lesions may also be seen.
4. *Immunophenotyping* – of the antigens present on the bone marrow or peripheral blasts is the most reliable method of determining whether the leukaemia is lymphoid or myeloid, and cytochemistry helps to confirm myeloid or monocytic origin.
5. *Cytogenetic and molecular studies* – often detect abnormalities within the leukemic clone that can have diagnostic or prognostic value, e.g. the Philadelphia chromosome, which is the product of a translocation between chromosome 9 and 22, the presence of which confers very poor prognosis in ALL.
6. *Lumbar puncture* – with CSF cyrospin is an important initial staging investigation to detect leukemic cells in CSF, indicating involvement of CNS.

Differential Diagnosis

1. *The two types of leukaemias* – are clinically indistinguishable except that in ALL there is a slightly greater tendency to lymphadenopathy. The clinical features of various subtypes of AML are similar, but patients with acute monocytic or myelomonocytic leukaemia may present with swollen gums, and those with acute promyelocytic leukaemia with a severe haemorrhagic disorder due to disseminated intravascular coagulation. T-cell leukaemia is predominantly a disease of males and is often associated with presence of a mediastinal mass. Distinction between lymphoblastic and myeloblastic leukaemia may be difficult on morphological grounds.
2. *Lymphadenopathy* – Infectious mononucleosis.
3. *Hepatosplenomegaly* – Myeloproliferative or lymphoproliferative disorder, myelodysplasia, metabolic storage or autoimmune disorders, visceral leishmaniasis.

Management

1. ***Chemotherapy*** – At presentation the tumour load is 10-12 cells. Chemotherapy can reduce this by 3-5 logs. Hence the patient has still 10^8 leukemic cells when the marrow examination shows complete remission. To achieve long-term cure, the patient hence needs further therapy. The initial high-dose chemotherapy in order to reduce leukemic cells to below the levels of morphologic detection is labelled *indutcion.* This is followed by another dose of chemotherapy to further reduce the leukemic burden – called *consolidation.* Low-dose chemotherapy administered for a period of 18 months to 2 years is described as *maintenance therapy.* High-dose chemotherapy given more than 6 months after induction is termed *late intensification* (Table 35).

Table 35: Chemotherapy for ALL and AML.

Phase	*ALL*	*AML*
Induction	Vincristine (iv)	Daunorubicin (iv)
	Dasatinib (if pH +ve ALL)	Cytosine arabinoside (iv)
	Prednisolone (po)	
	L-asparginase (iv)	
	or Daunorubicin (iv)	
	or Dauromycin (iv)	
CNS prophylaxis	Methotrexate (intrathecal)	
Consolidation	Daunorubicin (iv)	High dose Cytosine arabinoside (iv)
	Cytosine arabinoside (iv)	
	Etoposide (iv)	
	Methotrexate, 6-thioguanine	
	Dexamethasone	
Maintenance	Prednisolone (po)	*Post-remission therapy*
	Vincristine (iv)	Myeloablative therapy followed by BMT in relapse or those with high risk chromosomal changes
	6-mercaptopurine (po)	
	Methotrexate (po)	

Acute promyelocyic leukemia - Tretinoin (45 mg/m^2 per day orally until remission is documented) plus concurrent anthracycline-based (i.e. idarubicin or daunorubicin) chemotherapy. It leads to CR rates of 90-95%. Arsenic trioxide improved outcome, if used after achievement of CR and before consolidation therapy with anthracycline based chemotherapy.

2. ***Bone marrow transplantation*** –

BMT in ALL – Allogenic BMT is an option in adult ALL patients entering first remission who have an HLA - identical sibling, provided they are reasonably fit and < 55 years.

BMT in AML – In adult AML – Because intensive chemotherapy (particularly involving high-dose cytarabine) has been shown to achieve survival rates comparable with allogenic BMT in first remission, BMT reserved for refractory cases and those with poor cytogenetics. In patients without a suitably matched donor, high-dose chemotherapy with autologous transplantation of haemopoietic stem cells derived from peripheral blood or bone marrow is an alternative treatment strategy.

3. ***Supportive care***

(a) *Anaemia* – Hb level should not be allowed to fall below 8 g/dl by transfusing 4 units of packed RBCs. If platelet count is less than 10 × 10^9/litre, platelet transfusion should precede RBC transfusion to reduce risk of haemorrhage. (b) *Bleeding* – Transfusion of pooled or single donor platelets. (c) *DIC* (Most often with acute promyelocytic leukaemia) – Fibrinogen replacement, platelet transfusion twice daily and anticoagulation. (d) *Infection* – Good nursing, isolation, prophylactic GI tract decontamination, antibiotics. Attention to fluid balance. Topical fungal infections may be prevented by giving oral fluconazole or non-absorbable amphotericin. Pneumocystis jiroveci pneumonia is a considerable risk during ALL maintenance therapy; low dose co-trimoxazole prophylactically throughout. Herpes simplex infection – Acyclovir 200 mg 5 times/day. Cytomegalovirus infection – Combination of ganciclovir and immunoglobulin. (e) *Hyperuricemia* – can be prevented by adequate hydration, and pretreatment with allopurinol which should be continued until peripheral blood is cleared of blast cells.

CHRONIC LEUKAEMIAS

Chronic Myeloid Leukaemia

Chronic myeloid leukaemia (CML) is a clonal disorder of a pluripotent stem cell. Normal blood cell production is almost completely replaced by leukemic cells, which however still function normally. It can occur at any age but the peak incidence is at age 40-60 years. Most cases of CML occur sporadically, the only known predisposing factor is irradiation, e.g. Japanese survivors of atomic bomb and in patients who received radiotherapy for ankylosing spondylitis.

Pathogenesis

1. BCR - ABL fusion gene in erythroid, myeloid and megakaryocyte precursors.
2. Philadelphia chromosome, it is formed as a result of reciprocal translocation of genetic material between long arm of chromosome 22 and chromosome 9.

Clinical Features

Common

1. *Non-specific* – Loss of weight, fatigue, malaise, excessive perspiration (due to increase in metabolic rate).
2. *Splenomegaly* – Size of the enlarged spleen tends to correspond to total leucocytic count.
3. *Bleeding* – Excessive menstrual or other bleeding. Bruising or purpura may occur or spontaneous hematoma.
4. *Anaemia.*
5. *Bone pain* – due to extension of haemopoiesis throughout the long bones. Sternal tenderness.

Rare

- Splenic infarction
- Leucostasis
- Gout
- Retinal haemorrhages
- Priapism
- Fever

Differential Diagnosis

1. Leukaemoid reaction

Differentiation of Leukaemoid reaction and CML

	Leukaemoid reaction	**CML**
Splenomegaly	No	Yes
TLC	10-50 ×10^9/L	100-500 × 10^9/L
Toxic granules in neutrophils	+ ve	- ve
Basophilia	– ve	+ ve
Eosinophilia	– ve	+ ve
Ph chromosome	– ve	+ ve

2. Myelofibrosis (Refer)

Investigations

Peripheral blood – WBC count – 10-500 × 10^9/litre, with excess of neutrophils, myelocytes and blasts (Fig. 35). Basophilia and eosinophilia are prominent and thrombocytosis is common.

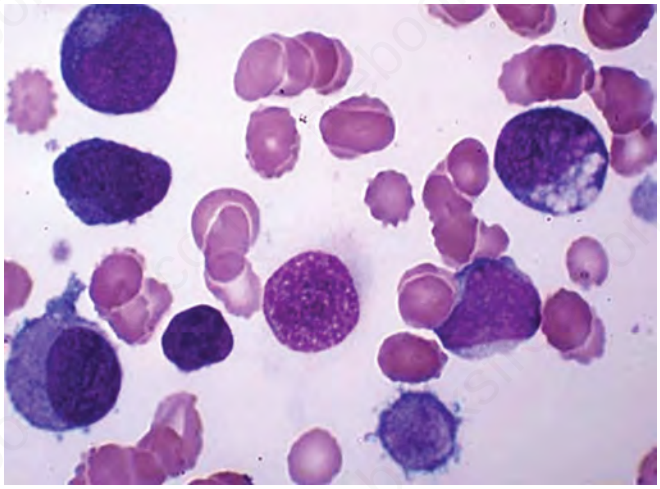


Fig. 35: Chronic granulocytic (myeloid) leukemia (peripheral blood). There is an increased number of granulocytes, most of which are mature neutrophils. A few more primitive cells are also present

Bone marrow – is hyercellular with marrow fibrosis and Gaucher like cells and the marrow or peripheral blood can be studied cytogenetically. High myeloid-to-erythroid ratio of 15-20:1.

Neutrophil alkaline phosphatase (NAP) – is low and is therefore useful in excluding reactive neutrophilia.

Serum vitamin B_{12}– increased

Serum uric acid – increased

Cytogenic analysis - documenting t(9;22) (q34;q11.2) seen in 90% patients.

Clinical course – After a chronic phase of an average 2-3 years duration, the disease enters an accelerated and then a blastic phase, the leukaemia cells of which can be immunophenotype as either myeloid (about 60%) or lymphoid (about 40%) in origin.

Treatment of Ph-positive CML

Chronic phase

1. *Tyrosine kinase inhibitor (TKI) therapy* with Imatinib 400 mg od as first line.
2. *Other 2nd generation* TKI advocated in first line therapy as alternative are Bosatinib and Nilotinib.
3. *Ponatinib* is a third generation TKI to be used in case of resistance to first or second generation TKIs, also recommended in activated phase and blast phase.
4. *Zinatinib* is now used in case of very high counts.
5. *Allogenic stem cell transplant* with HLA matched related or unrelated donor, recommended in case of TKI intolerance, resistance or on progression to accelerated or blast phase in combination with Ponatinib.

Matched-sibling allogenic SCT – Inspite of hazards, it is the only definite potentially curative treatment and should be offered to younger patients with CML who have an HLA - identical sibling.

Before transplantation, the patient undergoes a 'conditioning regimen' – busulphan followed by cyclophosphamide can be effective instead of cyclophosphamide followed by total body irradiation.

Relapse after allogenic BMT – The best method of treating patients who relapse is transfusion of T lymphocytes collected from the original donor by leukapheresis.

6. Omacetaxine, a protein synthesis inhibitor with presumed more selective inhibition of the synthesis of the BCR-ABL1 oncoprotein.

Advanced phase disease

Cl. Fs. – Excessive sweating, persistent fever, or otherwise unexplained symptoms of anaemia, splenic enlargement or infarction, hemorrhage or bone pain. In most cases the blast crisis is myeloid (resembling AML), and in a fifth of cases lymphoid blast crisis occurs.

Laboratory Fs. – (a) Rapid white cell doubling time. (b) WBCs poorly responsive to full doses of cytotoxic drugs. (c) Anaemia or thrombocytopenia. (d) Persistent thrombocytosis (> 100×10^9/L). (e) > 10 blasts in peripheral blood or marrow. (f) > 20 blasts promyelocytes in blood or marrow. (g) Acquisition of 'non-random' chromosomal changes in addition to presence of Ph chromosome.

Management:
Lymphoid blast crisis– Treatment similar to ALL.
Myeloid crisis – Prognosis is grave and few of the drugs used in treatment of AML offer more than temporary relief.

CHRONIC LYMPHOCYTIC LEUKAEMIA

Chronic lymphocytic leukaemia (CLL) is a heterogenous group of lymphoproliferative disorders due to accumulation of neoplastic lymphocytes in peripheral blood (Lymphocytic count > 10×10^9/L), > 30% lymphocytes. Mature lymphocytes in blood are monoclonal β cell.

Aetiology

a. Genetic factors - High incidence in some families.

b. TNF-α – CLL cells produces TNF-α and TNF-β which causes proliferation of leukaemia cells and transforming growth factor respectively.

c. IL-2 induces proliferation of CLL cells and inhibits apoptosis of these cells.

Clinical Features

- Asymptomatic – in about 25% and discovered on routine examination.
- Painless lymphadenopathy
- Infections – due to suppression of immunoglobulins – bacterial pneumonia and herpes virus infections.
- Symptoms due to bone marrow failure (anaemia, thrombocytopenia)
- Hepatosplenomegaly – in later phases of the disease
- Skin infiltration – with nodules or diffuse erythematous infiltration (hommerouge).

CLL is associated with autoimmune haemolytic anaemia and/or thrombocytopenia.

Treatment can be continued with Imatinib. In case of Imatidine resistance, second generation kinase inhibitors can be used, e.g. Dazatinib, Bosutinib, Nilotinib, or newer generation Penatinib.

Initial assessment should include:

- Complete family history of leukaemias and lymphomas
- Physical examination
- Blood cell and reticulocyte counts
- Lymphocyte morphology Immunophenotyping from bone marrow or peripheral blood
- ESR
- Renal and liver biochemistry
- Serum immunoglobulins
- Direct Coomb's test
- Bone marrow aspirate and trephine for cytogenetic study
- Chest radiography and abdominal ultrasonography and/or CT.

Other tests (e.g. lactic dehydrogenase (LDH), β_2-microglobulin, soluble CD23 levels), serum immunoglobulin levels.

Table 36 gives staging systems in CLL.

Table 36: Staging systems in CLL.

Staging	*Clinical features*	*Median survival, in years*
Rai system		
0: Low risk	Lymphocytosis only in blood and marrow	>10
I: Intermediate risk	Lymphocytosis + Lymphadenopathy	7
II: Intermediate risk	Lymphocytosis + Lymphadenopathy + splenomegaly ± hepatomegaly	7
III: High risk	Lymphocytosis + anemia	1.5
IV: High risk	Lymphocytosis + thrombocytopenia	1.5
Binet system		
A	Fewer than three areas of clinical lymphadenopathy; no anemia or thrombocytopenia	>10
B	Three or more involved node areas; no anemia or thrombocytopenia	7
C	Hemoglobin ≤10 g/dL and/or platelets <100000/μL	2

Investigations

1. ***Peripheral blood*** – (a) Lymphocytosis. CLL lymphocytes are small with clumped chromatin; larger nucleated cells (e.g. prolymphocytes) may be seen, but comprise less than 10% in typical CLL (Fig. 36). (b) Smudge (basket cells). Some of the lymphocytes rupture while making the peripheral smear.

   The immunophenotype of CLL is unique and distinct from other B cell disorders.

2. ***Liver and renal biochemistry***– are usually normal, but there may be hyperuricaemia, mildly raised serum LDH and β_2 - microglobulin, and hypogammaglobulinaemia. (Partly responsible for high incidence of infections).

3. ***Bone marrow aspirate***– (a) Hypercellularity. (b) Lymphocytic infiltration; this is confirmed on trephine biopsy, which allows assessment of the pattern of infiltration. Mature lymphocytosis is a diagnostic feature. (c) In course of time, the neoplastic lymphocytes replace normal cells of erythroid, myeloid and megakaryocytic cells.

4. ***Abdominal CT***– for lymphadenopathy, splenomegaly.

Transformation in CLL – (a) Richter's syndrome: Progressive splenomegaly lymphadenopathy, fever. Poor prognosis. (b) Prolymphocytic leukaemia. (c) Multiple myeloma.

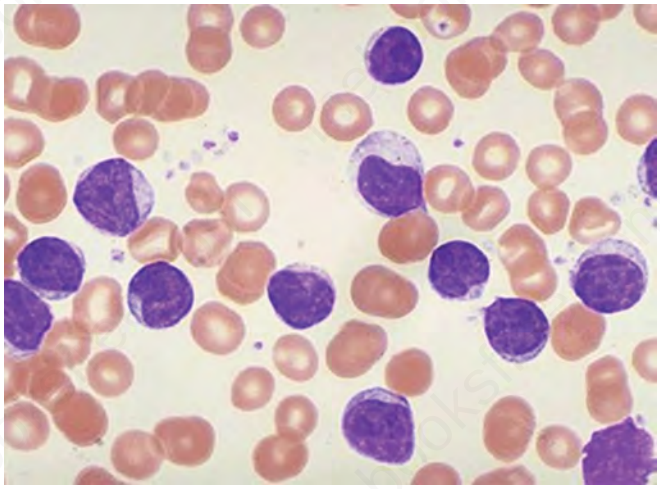


Fig. 36: Showing chronic lymphocytic leukemic cells

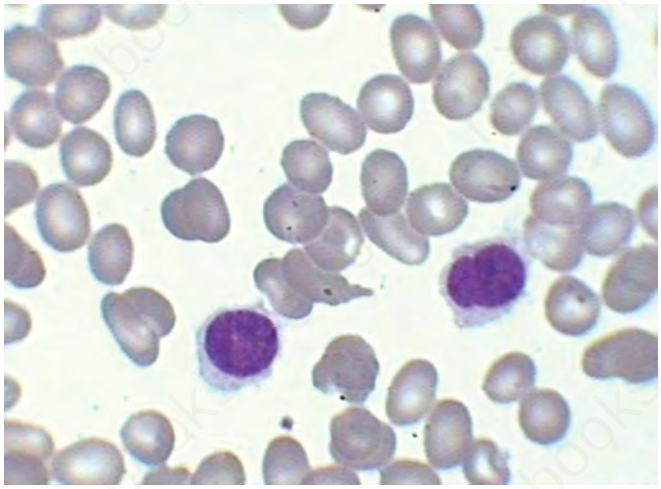


Fig. 37: Hairy projections on lymphocytes in hairy cell leukemia

Differential Diagnosis

1. Other B cell disorders (e.g. prolymphocytic leukaemia, lymphomas in leukemic phase)
2. T cell disorders and reactive T cell lymphocytosis (caused by virus infections or post-splenectomy)
3. Polyclonal B cell lymphocytosis

Treatment

Age < 70 or older patients without sequential comorbidities

- FCR Fludarabine, Cyclophosphamide, Rituximab
- FR Fludarabine + Rituximab
- PCR Pentostatin + Cyclophosphamide + Rituximab
- BR Bendamustine + Rituximab

Age ≥ 70 or patients with comorbidities even, if younger

- Chlorambucil ± Rituximab
- BR Bendamustine + Rituximab
- Cyclophosphamide, Prednisolone + Rituximab
- Alemtizumab
- Rituximab
- Fludarabine ± Rituximab

If with deletion (17p)

- FCR
- FR
- High dose methyl prednisolone + Rituximab
- Alemtuzumab ± Rituximab

Allogenic transplant an option for patients in CR/PR after chemotherapy.

Newer agents

a. Anti-CD20 monoclonal antibodies of atumumab and obinutuzumab, activity in previously treated patients.
b. Ibrutinib - an irreversible inhibitor of Bruton's tyrosine kinase, and
c. Idelalisib - an inhibitor of phosphoinositide- 3-kinase delta.

The ideal combination and sequence of these therapies have not been defined.

HAIRY CELL LEUKAEMIA (HCL)

Hairy cell leukaemia (HCL) is an old age B cell lymphoproliferative disorder characterized by presence of hairy cells in peripheral blood, pancytopenia and splenomegaly.

Cl. Fs. (a) Wt. loss, fatigue. Fever can be presenting symptom. (b) Splenomegaly moderate to massive. (c) Easy bruising (due to thrombocytopenia) and infections. (d) Hepatomegaly in 1/3 of patients.

Investigations

1. *Blood* - (a) Pancytopenia. (b) Hairy cells or Large-cells with fine cytoplasmic processes (hair on the cell surface) (Fig. 37). E/M reveals presence of hairy processes -Microvilli and rod shaped structures (ribosomal lamellar complexes) in cytoplasm. (c) Cytochemistry - TRAP (Tartarate resistant acid phosphatase) positivity in cytoplasm is characteristic of HLL. (d) Immunophenotyping CD19, 20 and 22 positive. CD25, CD11, CD103 positivity are pathognomonic of HCl.

2. *Bone marrow* (a) Aspirate - Dry tap in majority. (b) Trephine biopsy – Honey comb appearance due to infiltration by marrow cells. Each nucleus is seen separately resembling 'fried egg' (pathognomonic of HCl).
3. *Spleen* - Leukemic infiltration of red pulp.

Treatment

i. Cladiribine - Single cycle in dose of 1 mg/m^2/day infusion
ii. If no response to cladiribine, pentostatin 4 mg/m^2 by rapid IV injection or IV infusion in dextrose saline.
iii. Rituximab can be added to chemotherapy for better response.

PROLYMPHOCYTIC LEUKAEMIA (PLL)

Patients present with splenomegaly without lymphadenopathy and high rapidly rising lymphocyte count. Diagnosis is confirmed by a majority of prolymphocytes (twice the size of CLL lymphocyte) with large, central nucleolus. *Treatment* – Splenectomy usually of benefit and purine nucleoside may help.

ADULT T CELL LEUKAEMIA (ATLL)

Associated with human - T lymphocyte virus. *Clinical presentation* is often acute with mediastinal mass, massive splenomegaly, high TLC and hypercalcaemia. *Diagnosis* – ATLL lymphocytes have a convoluted, 'clover-leaf' nucleus and consistent CD4$^+$ phenotype. Prognosis is poor.

11. LYMPHOMAS

The lymphomas or reticuloses consist of diseases characterized by enlargement of lymph glands, splenomegaly, greater or lesser degree of constitutional disturbance and ultimately fatal outcome.

The following diseases are classified as malignant lymphomas:

1. Hodgkin lymphoma
2. Non-Hodgkin lymphoma
3. Multiple myeloma
4. Waldenstrom macroglobulinemia

CLASSIFICATION OF LYMPHOMAS

WHO classification of the mature B-cell, T-cell and NK-cell neoplasms.

Mature B-cell Neoplasms

- Chronic lymphocytic leukaemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Lymphoplasmocytic lymphoma b Waldenstrom's macroglobinaemia.

Plasma Cell Myeloma/Plasmacytoma

Extranodal marginal zone B-cell lymphoma of MALT type
Mantle cell lymphoma
Follicular Iymphoma
Nodal marginal zone B-cell lymphoma (± monocytoid B cells)
Diffuse large B-cell lymphoma (including subtypes)
Burkitt's lymphoma/Burkitt's cell leukemia
Primary mediastinal large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV-8+ multicentric Castleman's disease
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma

HODGKIN'S DISEASE

Hodgkin's disease is a clinically and histologically distinct lymphoproliferative disorder of unknown etiology. The type lymphocyte predominance is a clinically distinct B cell lymphoma often presenting with isolated enlargement of a peripheral lymph node. The nodal sclerosing type constitutes 70-80% of cases of the disease and classically presents with mediastinal and cervical node disease.

Aetiology

(a) *Age incidence* – Bimodal with peak incidence at 25 and another at 70. (b) *Sex* – More in males 1.5:1. (c) *Viruses* – Numerous serological and molecular studies have demonstrated an association between Epstein-Barr virus (EBV) infection and HD. In HD associated with EBV, the virus is localised to Reed-Sternberg cells, EBV latent gene products are expressed and the EBV infection is clonal. EBV association is strongest in children and the elderly with mixed cellularity HD, and more tenuous in young adults with nodular sclerosing HD. Lymphocyte-predominant HD is invariably negative. HIV-associated HD is invariably EBV positive and patients are more likely to be IV drug

abusers and have the mixed cellularity or lymphocyte-depletion subtype. (d) *Reproductive factors* – have a role in women. Parity is protective. (e) *Genetic factors* – Familial aggregation studies and HLA associations suggest an inherited susceptibility to HD. In young adults, almost 100-fold increase is seen in monozygotic twins, and a 7-fold increase in siblings. (f) *Other factors* – HD has occasionally been linked with certain occupations particularly exposure to wood dust. Occupational exposure to benzene and use of nitrous oxide as a dental anaesthetic are also possible risk factors.

WHO classifies Hodgkin's lymphoma as given in Table 37.

Histopathology

Most of the cells in the involved tissues are benign (95%) and Reed - Sternberg-like cells may be seen in various other reactive and malignant processes. Immunophenotyping is an important aid to diagnosis. In classical HD, scattered binucleate or multinucleated Reed-Sternberg cells and mononuclear Hodgkin's cells are seen, associated with a reactive cellular infiltrate of lymphoid cells, eosinophils and other inflammatory cells. (Fig. 38) The precise origin of Reed-Sternberg cells is unknown; they are thought to be derived from a lymphocyte lineage, though various studies report B, T or null cell characteristics.

Clinical Features

I. ***Local signs***– (a) *Lymphadenopathy* – Contiguous involvement of superficial lymph nodes in neck usually first to enlarge, at first one side, then the other. Sometimes axilla, groins, mediastinum or abdomen. Painless, leathery to feel and discrete. Characteristic appearance in advanced cases is a pyramidal swelling with its base at the clavicle and its apex at the angle of the jaw. When more than one region is involved, the areas are usually contiguous, suggesting that spread is predominantly through the lymphatics. Alcohol-induced pain in the nodes may occur but is rare. (b) *Splenomegaly* – in two-third cases, usually of moderate degree, occasionally marked. (c) *Hepatomegaly* – in 50%, moderate, non-tender enlargement of liver.

Involvement in Hodgkin's is usually seen above the diaphragm. Below the diaphragm is not seen commonly.

II. ***Systemic symptoms***

1. Cachexia and loss of weight. (10% of body weight. within 6 months prior to diagnosis).
2. Fever – (i) Mild grade remittent like tuberculosis most common or (ii) Undulant type of pyrexia of several days duration interrupted by periods of remission (Pel-Ebstein) or (iii) Continued type resembling typhoid.
3. Night sweats.
4. Pruritus generalized and refractory.
5. Infection – not uncommon. Herpes zoster, tuberculosis, or fungal disease.
6. Anaemia – may be due to haemolysis, hypersplenism, ineffective erythropoiesis, and haemodilution resulting from an expanded plasma volume.

III. ***Due to metastatic growths or infiltrations***

1. Skin – Pruritus, localized or generalized brownish eruption, erythema, herpes zoster, etc.
2. Bones – Localized pain and tenderness. Sclerotic deposits on radiography (ivory vertebrae).
3. Nervous system – Paraesthesia and pains. Diplegia or paraplegia.
4. Mediastinal pressure – Dyspnoea, cyanosis and stridor, dysphagia.
5. Respiratory tract – Laryngeal paralysis, collapse of lung, pleural effusion and bronchiectasis.

Table 37: WHO classification of Hodgkin's lymphoma.

• Nodular lymphocyte predominant Hodgkin lymphoma (<5%)
• Classic Hodgkin lymphoma (95%)
• Nodular sclerosis lymphoma
• Mixed cellularity lymphoma
• Lymphocyte-rich lymphoma
• Lymphocyte depleted lymphoma

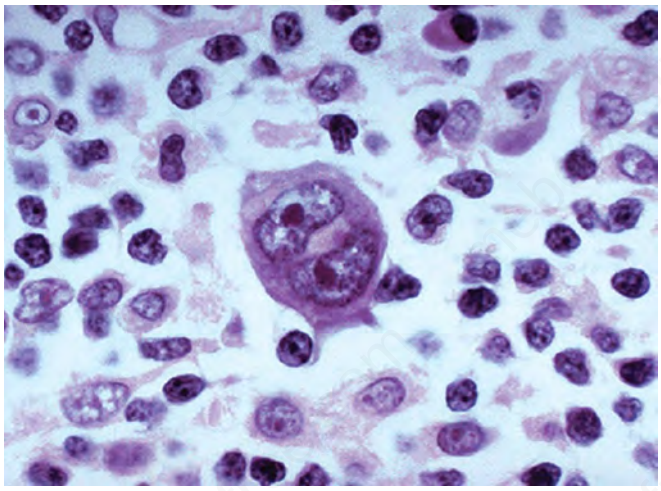


Fig. 38: Reed-Sternberg cell

6. Gastrointestinal – Intestinal obstruction, jaundice and ascites. Malabsorption due to obstruction of lacteals.
7. Genitourinary – Hematuria, pyuria, retention of urine, pain in the back, a mass in the flanks or symptoms suggestive of disease of prostate or testis.

IV. ***Due to immunologic changes***– (a) Lowering of resistance to infection. (b) Haemolytic anaemia.

Staging – Provides information of prognostic significance and selection of appropriate therapy:

Stage I: Involvement of single LN region or localized involvement of a single extralymphatic organ or site (IE).

Stage II: Involvement of 2 or more LN regions on same side of diaphragm (II) or localized involvement of a single associated extralymphatic organ or site or its regional LN with or without involvement of other LN regions on same side of diaphragm (IE). Number of LNs involved may be indicated by a subscript (e.g. II_3).

Stage III: Involvement LN regions on both sides of diaphragm (III) which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of spleen (IIIC) or both (IIIE,S).

Stage IV: Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated LN involvement, or isolated extralymphatic organ involvement with distal (non-regional) nodal involvement.

Suffixes are added to the anatomical stage

A No systemic symptoms

B Systemic symptoms - Unexplained fever >37°C, weight loss

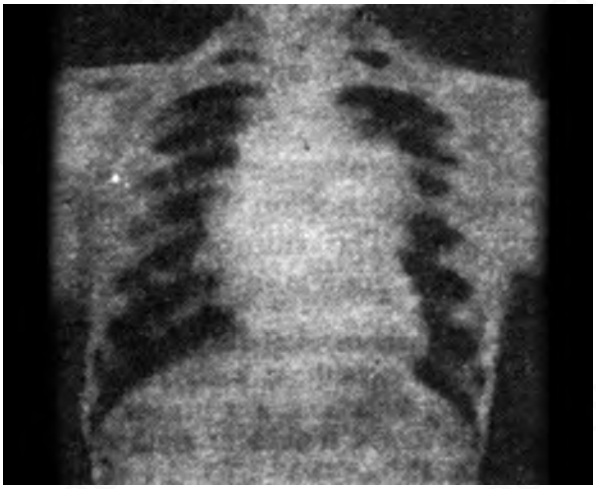


Fig. 39: Hodgkin's lymphoma. Masses of enlarged lymph nodes in the mediastinum. For causes of bilateral hilar enlargement (See chapter 16)

E Involvement of a single extranodal site, contiguous or proximal to known nodal site

X Bulky disease (>10 cm mediastinal mass)

Investigations

1. Laboratory investigations: (a) FBC: Nonspecific anaemia of chronic disease common, and lymphopenia (particularly of CD4 T cells). Eosinophilia in about 15%. (b) ESR commonly elevated and with LDH is a useful indicator of disease activity.
2. Lymph node biopsy: Excision biopsy is required where the entire LN removed and sent for analysis. It shows characteristic histology – (a) Presence of Reed-Sternberg cells (absence does not rule out Hodgkin's disease). (b) Pleomorphic pattern of cell types – lymphocytes, eosinophils and stroma which destroys normal architecture of the gland.
3. Imaging: (a) *Plain chest radiograph* [Fig. 5.12 (Fig. 39)]. (b) *PET* – CT is the most important baseline investigation for staging purposes, and to determine precise extent of disease. It can also detect presence or absence of bone marrow involvement after chemotherapy.
4. Bone marrow: Aspiration biopsy Indicated in stage II disease and higher staging.

Differential Diagnosis: See differential diagnosis of lymphadenopathies.

Table 38 gives differences between Hodgkin's disease and non-Hodgkin's lymphoma.

Management

1. **Early-stage disease** – Brief chemotherapy followed by involved field irradiation is the best choice for non-bulky clinical stage IA and IIA HD. IFRT is given to all sites of bulky disease post ABVD. Minimizing both chemotherapy and radiotherapy should reduce the risk of infertility, premature menopause, cardiovascular disease and second neoplasms.

Table 38: Differences between Hodgkin's disease and non-Hodgkin's lymphoma.

	Hodgkin's disease	*Non-Hodgkin's lymphoma*
Incidence	Stable	Increasing
Age	Median 29 years	Increasing
		Incidence with age
Sites	Nodal; supra-diaphragmatic	Nodal or extranodal; any site
Cl. Fs.	Mediastinal mass, itching, alcohol-induced pain	Nil specific
Prognosis	70-80% cure	Highly variable by type; most incurable

Table 39: ABVD combination.

Drug	*Dosage*
Adriamycin (Doxorubicin)	25 mg/m^2 IV days 1 and 15
Bleomycin	10 unit/m^2 IV days 1 and 15
Vinblastin	6 g/m^2 IV days 1 and 15
Dacarbazine	375 mg/m^2 IV days 1 and 15

2. **Advanced-stage disease** – is treated with combination chemotherapy. ABVD (Table 39) has replaced MOPP (risk of leukemia with this regimen) as the standard regimen. ABVD has less long-term toxicity (including sterility and second malignancy), though other toxicities (e.g. pulmonary fibrosis, cardiomyopathy) may occur, particularly when ABVD is given with radiotherapy.

However, combined modality therapy is considered standard treatment in patients with bulky mediastinal HD followed by involved field radiotherapy (IFRT).

Give 12 cycles with 2 week's rest between the end of one course and beginning of next (1 course = 2 cycles).

Disadvantages: Acute toxicity, febrile neutropenia and potential long-term side-effects (infertility pulmonary fibrosis and second malignancy, including AML).
Advantage: Better overall response rates and less likely to cause sterility.

Alternating MOPP with ABVD gives very good response.

Immunotoxin, brentuximab vedotin, that selectively targets cells expressing CD30 can be combined with ABVD regimen.

Therapy for relapse: High-dose therapy and autologous stem cell transplantation is standard treatment for HD in first or subsequent post-chemotherapy relapse.

Long-term Complications and Treatment

- About 30% men are infertile at presentation, but sperm banking should be considered even in those with low sperm count before systemic chemotherapy is given.
- Amenorrhoea develops in about 25-75% of young females.
- Mantle irradiation can cause acute radiation pneumonitis and chronic lung damage.
- About one-sixth of patients cured of HD develop a second malignancy within 15 years of treatment, such as AML, NHL and solid tumors often within the radiation field (lung, breast).

NON-HODGKIN'S LYMPHOMA (NHL)

NHL is a heterogenous group of malignant diseases characterized by replacement of normal lymphoid structure by diffuse and nodular collections of abnormal lymphocytes.

Classification of Non-Hodgkin Lymphoma (NHL)

Mature T-cell and NK-cell Neoplasms

- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia b Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK cell leukaemia
  - Systemic EBV positive T-cell lymphoproliferative disorder of hildhood
  - Hydroa vacciniforme-like lymphoma
  - Adult T-cell leukemia. lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
  - Sezary syndrome
  - Primary cutaneous CD30 positive T-cell lymphoproliferative disorders b Lymphomatoid papulosis b Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous CD8 positive aggressive epidermotropic
  - Cytotoxic T-cell lymphoma
  - Primary cutaneous CD4 positive small/medium T-cell lymphoma
  - Peripheral T-cell lymphoma, NOS
  - Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK positive
  - Anaplastic large-cell lymphoma, ALK negative

Aetiology – in most cases is unknown.

Predisposing Factors

1. **Infections**
   - Bacterial (e.g. *H. pylori*)
   - Viral (e.g. human T cell lymphocytic virus 1, E-B virus), hepatitis C infection.
2. Immunodeficiency
   - Immunosuppressive therapy (post-transplantation)
   - HIV infection
3. Autoimmune disorders
4. Ionizing irradiation
5. Carcinogenic chemicals
6. Inherited disorders
   - Ataxia telangiectasia
   - Xeroderma pigmentosum

- Bloom's syndrome
- Fanconi's syndrome
- Immunodeficiencies (e.g. Wiskott-Aldrich syndrome)

Clinical Features

- *Painless lymphadenopathy* – often widespread and not necessarily contiguous
- *Constitutional (B) symptoms* – fever, sweats, anorexia, weight loss
- *Respiratory symptoms* – from pleural effusion, mediastinal node enlargement or parenchymal lung involvement
- *Involvement of other sites* – (a) Skin – Sezary's syndrome/mycosis fungoides. (b) Tonsils and adenoids. (c) Salivary glands. (d) Gastrointestinal tract. (e) CNS – HIV- related and lymphoblastic. (f) Jaw – Burkitt's lymphoma and (g) Testis.

Investigations

Laboratory Features

Haematology – The following may be observed, particularly in more advanced disease:

- Normochromic, normocytic anaemia
- Leucoerythroblastic anaemia (bone marrow infiltration)
- Hypersplenism
- Neutropenia and thrombocytopenia
- Autoimmune cytopenias (direct antiglobulin test positive)
- Circulating lymphoma cells (follicular, mantle cell and large cell lymphomas)
- Raised ESR/C-reactive protein. Raised LDH, LDH correlates with disease load.

Biochemistry

- Raised LDH and hypoalbuminemia (Features of advanced disease and of prognostic significance)
- Paraproteins (IgM, IgG or IgA) more common in indolent lymphomas
- β_2-microglobulin may be elevated especially in myeloma
- Normal immunoglobulins reduced
- Hypercalcemia often seen in ATLL and myeloma
- Abnormalities of liver or kidney function may reflect involvement with disease

Immunohistochemistry: Detection of immunological markers, which may be performed on circulating lymphoma cells or on fixed tissue sections from lymph nodes or other sites is essential for diagnosis and classification.

Molecular biology: Clonality of tumours may be demonstrated using Southern blot or polymerase chain reaction analysis to detect immunoglobulin and T cell receptor gene arrangements. Specific translocations have been identified in certain NHL subtypes and can be helpful in diagnosis.

Diagnosis and Staging

Diagnosis – is based on history, examination and histology. The morphological, immunological and cytogenetic characteristics of histological material obtained from excision biopsy of lymph node or extranodal tumour help in determining the type of NHL.

- PET- CT first line most important investigation can detect bone marrow involvement
- Bone marrow aspirate and trephine biopsy
- Examination of oropharynx (Waldeyer's ring), particularly in primary gastrointestinal NHL
- Lumbar puncture in high-grade lymphoma
- Liver biopsy, MRI as indicated

Staging – is essentially same as for Hodgkin's disease.

Differential diagnosis is usually from other causes of lymphadenopathy

1. Hodgkin's lymphoma
2. Infection – Tuberculosis, EBV, cytomegalovirus, HIV, toxoplasma, histoplasmosis
3. Autoimmune disease – RA, SLE
4. Sarcoidosis
5. Carcinoma
6. Leukaemia

Treatment

Low grade lymphoma

'Watch and wait' policy until there are indications for active treatment:

- B symptoms. Organ involvement compromising its function
- Bone marrow failure
- Bulky disease
- Disease progression.

Treatment given with R-CHOP (Table 40) in B-cell NHL and CHOP alone in T-cell NHL (commonly but other regimens can be used depending on type of lymphoma).

Response depends on type of lymphoma

R: Bendamustine used in Follicular + Mantle cell NHL
FCR: Fludarabine, Cyclophosphamide, Rituximab

Table 40: R-CHOP regimen.

- Rituximab 375 mg/m^2/day
- Cyclophosphamide 750 mg/m^2/day
- Adriamycin 50 mg/m^2/day
- Vincristine 1.4 mg/m^2/day (Max. 2 mg)
- Prednisolone 100 mg/m^2 × 5 days
  Given every 21 days × 6 cycles.

Intermediate-grade

Stage I disease – (Follicular NHL only) can be controlled by radiotherapy alone in upto 80% of patients. Addition of chemotherapy for patients with poor prognostic factors (e.g. bulky disease, B symptoms, raised LDH).

Stage II-IV disease – Combination chemotherapy such as R-CHOP which has the advantage of being relatively well tolerated and easily administered.

The outlook is poor in those in whom initial therapy fails because of resistance or relapse. Salvage therapy with autologous bone marrow transplantation is successful only in patients who remain sensitive to cytotoxic drugs, and is superior to conventional dose chemotherapy.

High-grade Lymphoma

CNS-directed prophylactic therapy (i.e. systemic high dose and/or intrathecal methotrexate) is required because of the high risk of CNS disease.

ALL regimens are generally used. In poor-risk patients, high-dose therapy and bone marrow transplantation during first remission.

Rituximab (Anti-CD20 monoclonal antibody).
3 weekly in combination with chemotherapy in a dose of 375 mg/m^2 in 500 ml normal saline after premedication (oral paracetamol with steroid and antihistamines). The infusion is started at 5 mg/hr for first one hour. If no reaction, infusion rate is increased so as to complete it over 3-4 hours.

Use of Rituximab is recommended in all lymphomas with CD20 +ve.

Extranodal lymphomas – occur in about 25% of patients. (a) Gastric MALT lymphoma may respond to anti-*Helicobacter* therapy alone. (b) Monocytoid B cell lymphoma often arises in the salivary glands and is associated with Sjogren's syndrome. (c) Cutaneous T cell lymphoma responds to skin-directed therapy such as psoralen, ultraviolet A therapy, electron beam therapy and photophoresis.

Table 41 summarizes chemotherapy regimens in non-Hodgkin's lymphoma.

Table 41: Chemotherapy regimens in non-Hodgkin's lymphoma.

Single agents	*Dose/Route/Days*
Cyclophosphamide (every 1-2 wks)	500 mg/m^{2}po/iv 1
Fludarabine (4 wkly)	25 mg/m^{2}iv 1-5
Combination therapy	
CHOP (3 wkly)	
• Cyclophosphamide	750 mg/m^{2}iv 1
• Doxorubicin	50 mg/m^{2}iv 1
• Vincristine	1.4 mg/m^2 (max. 2 mg) iv 1
• Prednisolone	10 mg po 1-5
CVP (3 wkly) (in elderly pts.)	
Cyclophosphamide	720 mg/m^{2}iv 1
Vincristine	1.4 mg/m^2 (max 2 mg)
Prednisolone	100 mg po 1-5
FMD	
• Fludarabine	25 mg/m^2 iv 1-3
• Mitoxantrone	10 mg/m^2 iv 1
• Dexamethasone	20 mg/m^2 po/iv 1-5
PMITCEBO (continuous)	
• Mitoxantrone	7 mg/m^2 iv 1
• Cyclophosphamide	300 mg/m^2 iv 1
• Etoposide	150 mg/m^2 iv 1
• Vincristine	1.4 mg/m^2 (max. 2 mg) iv 8
• Bleomycin	10 mg/m^2 iv 8

Supportive care – Patients must be warned about possible side-effects of treatment. In the short-term, these include nausea, hair loss, bone marrow suppression, mucositis and tumour lysis syndrome. Patients may require antiemetics, infection prophylaxis and transfusion support. Initiation of chemotherapy in patients with high tumour load can result in rapid cell lysis, which may lead to metabolic disturbances. This can be largely avoided by adequate hydration (4 litres/day), allopurinol 300 mg od, and alkalization may be necessary. Infections should be treated with iv antibiotics. Folinic acid is given to reduce toxicity of high dose methotrexate. Growth factors to accelerate neutrophil recovery.

MULTIPLE MYELOMA

Multiple myeloma (MM) is a malignant disease of plasma cells in the bone marrow. It is characterized by excess production of a monoclonal immunoglobulin molecule, which can be detected in the serum, urine or both, and is

often associated with bone pain, anaemia and kidney failure, hypercalcaemia.

The incidence increases with age, most patients are over age of 60 years. The cause is unknown in most patients, though exposure to radiation is known to increase the risk.

PATHOGENESIS

For unknown reasons, one clone of plasma cells overgrows and produces one particular immunoglobulin molecule (a monoclonal immunoglobulin or paraprotein).

1. **Proliferation** of plasmoblasts plasma cells.
2. **IL-6** – plays an important role in proliferation of plasma cells and also lytic lesions of bones. It is also responsible for anaemia due to inhibition of erythropoiesis.
3. **Kaposi sarcoma associated herpes virus (KSHV)** in dendritic cells secret IL-6.
4. **Pre-existing MGUS** (monoclonal gammopathy of uncertain significance) predisposes to development of MM.
5. **Chronic exposure to low dose irradiation,** e.g. in workers of nuclear power plants, uranium mines.
   - In 80% of patients, there is a paraprotein in the serum, usually of the IgG or IgA class. The abnormal cells may also produce free light chains, small enough to cross the glomerulus, and pass into the urine as Bence-Jones protein, often causing tubular damage.
   - In 20% of patients, free light chains are only produced (Bence-Jones-only myeloma) and there is no paraprotein in the serum (free light chain disease). Non-secretory myelomas are now known to consist of excess free light chain disease and are usually seen in elderly patients. Commonly diagnosed when a patient suddenly develops ARF or is detected with unexplained rise in serum creatinine. Also can be detected when a patient has reduced Hb with no obvious cause.

CLINICAL FEATURES AND COMPLICATIONS

1. **Bone disease**
   - Bone pain is the most common presenting symptom
   - Pathological fractures
   - Generalized osteoporosis may lead to compression fractures of vertebrae causing back pain and occasionally cord compression. The cause of bone destruction is activation of osteoclasts by cytokines (e.g. tumour necrosis factor TNF) produced by malignant plasma cells; the osteoclasts secrete interleukin-6 (IL-6), a growth factor for plasma cells.
2. **Anaemia** is a common presenting feature.
3. **Kidney failure.** It is most commonly caused by Bence-Jones protein, which damages the tubules as it passes through the kidneys. Other factors that can cause or contribute to renal failure include hypercalcaemia, infection, and dehydration.
4. **Infections** – due to impaired humoral and cell-mediated immunity leading to increased susceptibility to bacterial and virus infection. Chest infections common.
5. **Neurologic –** Spinal cord/root compression.
6. **Due to M-proteins**
   - Cryglobulinemia
   - Hyperviscosity affects CNS, retina, CVS
   - Bleeding tendency - due to adhesion and aggregation of platelets
   - Coagulation cascade affection from formation of complexes with factors V, VII, VIII, I, II.
7. **Amyloidosis.** About 10% of patients develop primary (AL) amyloidosis. The kidney is usually affected; deposition of amyloid in the glomeruli leads to generalized proteinuria and nephrotic syndrome. Peripheral neuropathy (particularly carpal tunnel syndrome) and CHF may occur.
8. **Metabolic disturbances** If ARF – hypernatremia, hyperphosphatemia
9. **Constitutional symptoms**
   - Weight loss
   - Fever
   - Malaise
10. **Asymptomatic patients.** Diagnosis following finding of raised ESR or abnormal protein electrophoresis on routine screening or investigation for an unrelated problem.

Investigations

1. **Blood**
   - Reduced Hb. TLC and PLT usually normal
   - Rouleaux formation due to increased globulins
   - Serum B_{12} microglobulin is useful prognostic marker and is usually raised
   - Hypercalcemia
   - Kidney function tests – Raised serum urea, creatinine, uric acid and potassium

2. **Bone marrow** (Fig. 40)
   - Increased number of myeloma cells >10% diagnostic. M0yeloma cell is large in size with round to oval eccentric nucleus and pale blue cytoplasm. But may be normal as bone marrow investigation is usually patchy. Bone marrow biopsy is difficult due to extremely soft and spongy nature of the bones.
   - Some cases show "flame cells" with peripheral cytoplasm sowing flare, "grape cells" showing rounded immunoglobulin inclusions, and "Russel bodies" in the cytoplasm.
3. **Skeletal survey with X-rays of long bones, skull** (Fig. 41)**, vertebrae** (Fig. 42)**.**
4. **Serum and urine protein electrophoresis.**
5. **Serum immunofix and free light chain ratio.**
6. **24-hour urine for immunofixation.**
7. **Bence-Jones protein in urine.**

Smouldering syndrome – (a) 'M' proteins in serum >30 g/L and/or BM plasma cells >10%. (b) No related organ impairment, no tissue lesion.

Active myeloma requires one or more of the following:
Calcium >11.5 g/dl
Creatinine >2 mg/dl
Anaemia <10 g/dl or 2 g/dl < normal.

Diagnostic criteria for multiple myeloma are listed in Table 42.

Diagnosis of myeloma requires minimum of one major and one minor criteria that must include 1+2.

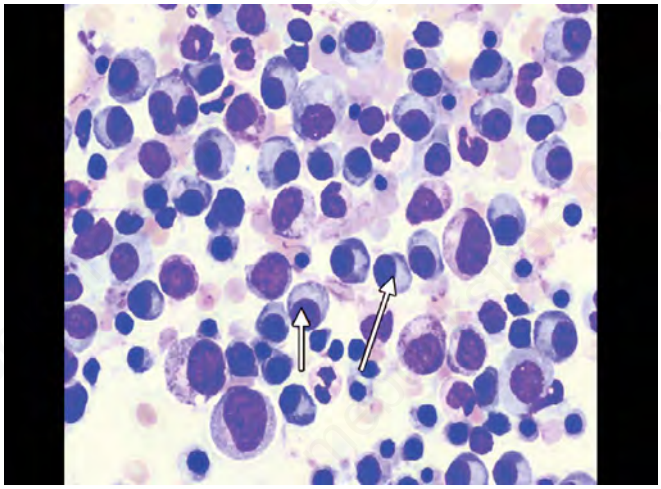


Fig. 40: Plasma cells, in bone marrow in multiple myeloma. Note: The plasma cells (arrows)

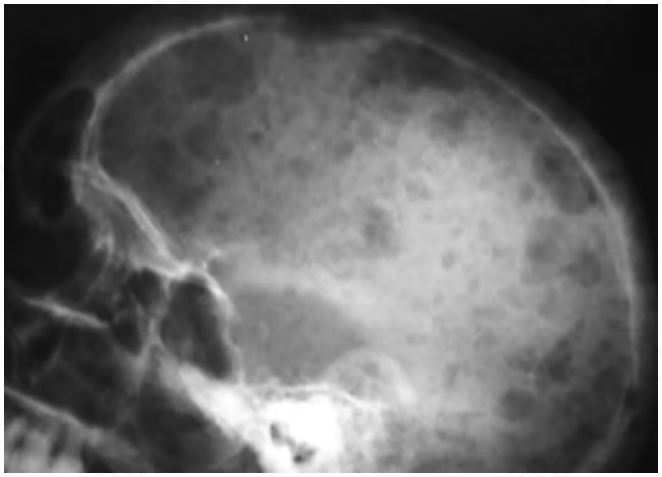


Fig. 41: X-ray skull showing multiple lytic lesions suggestive of multiple myeloma

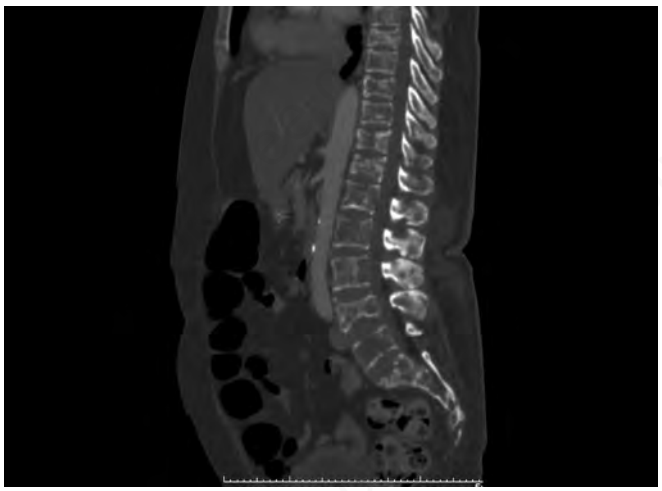


Fig. 42: Multiple Myeloma Spine

Table 42: Diagnostic criteria for multiple myeloma.

Major criteria	*Minor criteria*
1. Plasmocytoma on tissue biopsy	1. Bone marrow plasmolysis with 10-30% plasma cells
2. Bone marrow plasmacytosis with > 30% plasma cells	2. Monoclonal spike present, but less than levels defined
3. Monoclonal globulin spike on serum electrophoresis: IgG > 35%, IgA > 20 g/L. Light chain excretion on urine electrophoresis 1 g/24 hrs in absence of amyloidosis	3. Lytic bone lesions
	4. Normal IgM < 500 mg/L IgA < 1g/L or IgG < 6 g/L

Diagnosis of myeloma requires minimum of one major and one minor criteria that must include 1+2

Differential Diagnosis

- Cirrhosis, TB, AILD (angioimmunoblastic lymphadenopathy with dysproteinemia)
- MGUS (monoclonal gammopathy of uncertain significance)
- Waldenstrom's macroglobulinemia

Management

1. Immunomodulation – with drugs like Pomiabdomide, lenalidomide. Thalidomide is now used usually in combination with Bortezomib, and Dexamethasone.
2. Proteosome inhibitors – Bortezomib (first generation), Corplazomib (second generation). Lenalidomide 25 mg/day in patients with newly diagnosed MM is highly effective.
   Recommended combinations
   - Bortezomib + Lenalidomide + Dexamethasone or Bortezomib + Thalidomide + Dexamethasone
   - Other drugs used in combination

     Melphalan, Liposonasonabid, Doxorubicin + Cyclophosphamide
3. Autologous transplant – For second line therapy in refractory case. Can be used as alternative to above agents with similar results.
4. Bisphosphonates – Used monthly as part of all treatment regimes in myeloma patients.
5. Autologous BM transplantation carries a low risk and is suitable for patients upto 65 years of age. Duration of remission and survival appear to be prolonged compared with conventional chemotherapy.
6. Stem cell transplantation – Peripheral blood cell (PBSC) accelerate myelopoiesis.

With the new drugs available, transplant can now be used as a salvage therapy, as survival rates are equivalent.

Supportive Treatment and Treatment of Complications

Bone disease – (a) Localized radiation is used to treat painful bony lesions, pathological fractures and myelomatous tumors that impinge upon vital structures. (b) Bisphosphonates inhibit osteoclastic activity. Zoledronic acid given in a dose of 90 mg by 4 hour. iv infusion every 4 weeks. With this the incidence of pain, analgesic usage, skeletal events become significantly less.

Renal failure– can often be prevented by high fluid intake, correcting dehydration and treating hypercalcaemia. Patients with established renal failure may need dialysis. Early initiation of this may improve the likelihood of recovery of renal function.

Anaemia – usually improves when the disease responds to treatment. Blood transfusions may be needed, if anaemia is severe.

Infection – should be treated promptly and vigorously. Patients should be given influenza vaccine annually.

Prognostic Factors

- Tumour load – (a) Myeloma staging of tumour burden. (b) Serum microglobulin levels. Higher levels bad prognosis. (c) Other factors for poor prognosis – (i) Serum creatinine levels. (ii) Morphology of plasma cells. (iii) Diffuse plasma cell infiltrate in BM trephine biopsy.

Related Disorders

Localized plasmocytoma– Collection of plasma cells at single site. Usually part of generalised myeloma but isolated tumors can occur, most often in upper air passages and less likely to disseminate than those in the bone.

Benign paraproteinemia and indolent myeloma– Paraprotein concentration is less than 30 g/L and bone marrow contains less than 5% plasma cells. Some cases of benign monoclonal gammopathy may progress to multiple myeloma.

Plasma cell leukaemia– In peripheral blood more than 2×10^9 plasma cells/litre can occur at presentation, or in terminal phases of multiple myeloma. Associated with aggressive clinical course, soft tissue deposits and marrow failure.

Waldenstrom's macroglobulinemia– A rare disease low grade lymphoplasmocytic lymphoma occurring in the elderly, an IgM paraprotein is responsible for the disease, which in some cases leads to hyperviscosity syndrome causing impairment of retinal and cerebrovascular blood flow. *Cl. Fs.* (a) Pallor. (b) Mucosal bleeding. (c) Lymphadenopathy. (d) Hepatosplenomegaly. (e) Raynaud's phenomenon. (f) Diffuse osteoporosis.

Management – (a) Combination chemotherapy- Bendamustine and Bortezomib; Rituximab can be added to this combination (b) Plasmapheresis, if hyperviscosity syndrome.

Heavy chain disease (HCD)– Rare B cell proliferation in which there is secretion of heavy chains uncoupled with light chains. γ-chain disease starts with diffuse infiltration of the gut and may evolve into gut associated lymphoma. Palatal oedema can cause dyspnoea. There is lymphadenopathy, fever, anaemia M component is < 20 g/L. Rapidly progressive.

Cryoglobulinemia– Cryoglobulins are immunoglobulins which precipitate when cooled. Their presence may give rise clinically to Raynaud's phenomena, acrocyanosis, arthralgia, purpura and in severe cases isolated neurological lesions, kidney failure and hepatic failure.

POEMS syndrome– Rare variety of multiple myeloma consisting of polyneuropathy, organomegaly, endocrine disorders, monoclonal proteins and skin changes. Prednisolone 25-60 mg/m^2 BSA/day may be added in older patients but should be discontinued as soon as remission is achieved (50% reduction in paraproteins).

HAEMOPHAGOCYTIC LYMPHOCYTOSIS

HLH is a rare but potentially life-threatening condition characterized by uncontrolled activation of macrophages and lymphocytes. Paediatric age group is most commonly affected but if can occur at any age. It is not a single disease and can be encountered with a variety of underlying diseases (Table 43).

The pathological hallmark of the syndrome is excessive proliferation of macrophages and histiocytes which phagocytise other blood cells leading to the clinical symptoms (Fig. 43).

Clinical picture of HLH can be induced by a number of infectious organisms - viruses, (EBV, HIV, human herpes virus 8), mycobacteria and fungi. Most commonly associated malignancy is lymphoma. HLH has also been described in association with inborn error of metabolism like Lysinuric Protein Intolerance (LPI).

Table 43: Classification of haemophagocytic lymphocytosis.

1. *Inherited*
• Known genetic defects (perforin, syntaxin 11)
• Unknown genetic defects
• Immune deficiency syndrome
• Chediak Higashi syndrome
• X-linked lymphoproliferative syndrome
2. *Acquired*
• Exogenous agents (infectious organisms, toxins)
• Infection - Associated Haemophagocytic syn.
• Endogenous
– Rheumatic diseases
– Macrophage activation syndrome

12. BLOOD TRANSFUSION

INDICATIONS FOR THE USE OF BLOOD AND BLOOD PRODUCTS

Whole Blood Packed RBCs

1. *Acute blood loss*
   - > 20% of blood volume loss – trauma, surgery, GI bleeding
2. *Treatment of symptomatic anaemia*
   - Investigate cause and treat appropriately.
   - Symptoms should be the guide not haematocrit
3. *Bone marrow failure*
   - Caused by bone marrow disease
   - During chemotherapy and/or radiotherapy, including bone marrow transplantation
4. *Thalassemia*
   - Other inherited transfusion-dependent anaemia
5. *Exchange transfusion*
   - Neonates with haemolytic disease of the newborn
   - Adults with sickle cell disease
   - Severe falciparum malaria

In an average adult, 1 unit of whole blood or 1 unit of RBCs (250-300 ml) raises Hb by 1g.

Fresh Frozen Plasma

1. *Acquired coagulation defects*
   - With clinical evidence of bleeding
     Massive blood transfusion

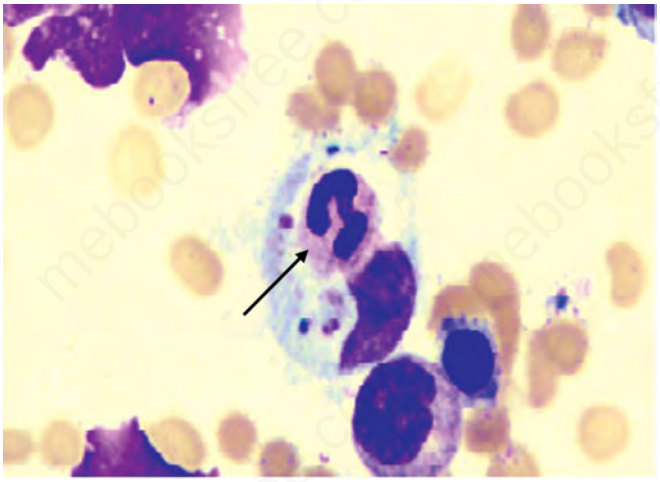


Fig. 43: Hemophagocytosis-of-neutrophil by macrophage. Note the engulfed neutrophil (arrow)

Advanced liver failure
Disseminated intravascular coagulation
Patients on oral anticoagulants
- Need for emergency invasive procedure when other interventions are too slow or ineffective

2. *Plasma exchange*
   - Thrombotic thrombocytopenic purpura
3. *Inherited coagulation defects*
   - If no specific coagulation factor concentrate

Platelets

1. *Therapeutic transfusion in patients who are bleeding*
   - Platelet count < 10×10^9/litre
   - Following massive transfusion with dilutional thrombocytopenia
   - Diffuse intravascular bleeding (correction of any coagulopathy)
   - Platelet dysfunction caused by drugs (aspirin) or congenital platelet disorders
2. *Prophylactic transfusion in thrombocytopenia*
   - Acquired bone marrow failure caused by bone marrow disease or chemotherapy/radiotherapy.
     Transfusion, if platelets < 10×10^9 litre (or < 20×10^9/litre if other risk factors)
   - To cover surgery in thrombocytopenic patients
     Major surgery (complex cardiac surgery, liver transplantation) > 80×10^9/litre
     Other invasive procedures > 50×10^9/litre
     1 unit of platelets (1 pool) is the dose for an average adult

Cryoprecipitate

1. *Acquired coagulation defects*
   - With clinical evidence of bleeding
   - Low fibrinogen may be useful guide:
     - Usually follows use of fresh frozen plasma
     - Massive blood transfusion
     - Disseminated intravascular coagulation
     - Advanced liver failure
2. *Chronic kidney failure*
   Helps control bleeding
3. *Inherited platelet function disorders*
   Helps control bleeding, if bleeding time is prolonged
4. *Inherited coagulation defects*
   - If no specific coagulation factor concentrate

   An adult dose is 10-20 donor units

Table 44 summarizes of indications for use of blood components.

COMPLICATIONS OF BLOOD TRANSFUSION

1. *Haemolytic reactions*: Due to ABO incompatibility with destruction of donor cells
   a. Immediate (Serious) – Fever with chills, backache, breathlessness, tachycardia and hypotension.
   b. Delayed (Mild) – 2 to 4 weeks later with fever, icterus and anaemia.
2. *Infections*
   - HIV can be transmitted by both plasma and cells
   - Hepatitis B and C (now rare because of proper screening)
   - Malaria
   - Yersinia and pseudomonas
   - Cytomegalovirus infection
   - Chagas' disease
   - Babesiosis
3. *Febrile reaction* – Onset of fever within ½ - 1 hr due to sensitization due to white cell antigens.
4. *Allergic reaction* manifests as urticaria, bronchospasm and rarely anaphylaxis.
5. *Circulatory overload* may result in acute pulmonary oedema in elderly and in pregnancy.
6. *Transfusion siderosis* (iron overload) can occur in thalassemia, aplastic anaemia and pure red cell aplasia. Iron is deposited in spleen, liver, heart, bone marrow.
7. *Physical effects of transfusion*
   - Thrombophlebitis is common in cases with indwelling catheters
   - Air embolism is now rare because of plastic bags and closed tubing system

Table 44: Summary of indications for use of blood components.

Component	*Indications*
1. Whole blood	• Acute hemorrhage
	• Exchange transfusion
2. Red cells (PCV 70%)	• Severe anaemia
3. Platelets in plasma < 10,000	• Thrombocytopenia
4. Fresh plasma 200-300 ml	DIC and multiple factor deficiencies
5. Cryoprecipitate	• Burns
5-15 ml containing	• Haemophilia
100U FVIII and	• Fibrinogen deficiency
200 mg fibrinogen	• Von Willebrand's disease

8. *Transfusion associated Graft versus Host disease* – In an immunocompromised patient, mature T cells act as immunocompetent cells in the graft and mount GVHD in an immunocompromised host.
9. Transfusion related acute lung injury (TRALI)– Patient develops non cardiogenic pulmonary oedema with bilateral chest infiltrate on X-ray and hypoxia during or within 6 hours of transfusion.

Plasmapheresis – is a procedure used to reduce plasma concentration of proteins, lipids, protein-bound hormones or toxins, antigens, antibodies or immune complexes. *Indications* – Symptomatic hyperviscosity syndrome main indication. Also myasthenia gravis (selected cases), thrombotic thrombocytopenic purpura, Goodpasture's syndrome, immune-complex mediated vasculitis. One to two plasma volumes can be exchanged in 1-3 hours.

13. ANTIPLATELET DRUG THERAPY

Platelet activation and aggregation play the central role in the normal haemostasis and disorders of thromboembolism. The mass aggregation of platelets form plugs, which, together with vessel constriction, maintains haemostasis in small vessels until the platelet plug is reinforced by fibrin.

An important aspect of platelet function and contribution to thrombus formation is their interaction with vascular endothelium. Injury to endothelium leads to adhering of platelets to subendothelial collagen and their activation. Platelets also release thromboxane, prostaglandin (PG) G_2 and H_2 and ADP which act as mediators to activate the platelets. Table 45 summarizes antiplatelate agents.

Table 45: Antiplatelet drugs.

Drug	*Dose*	*Mode of action*	*Comments / Adverse-effects*
Aspirin	75-325 mg/d	Inhibition of platelet prostaglandin synthesis Unopposed action of prostacyclin	Upper GI disturbances, increased risk of haemorrhagic strokes
Ticlopidine	250 mg bd	Inhibition of ADP-mediated platelet activation and release of platelet granule constituents and prolongation of bleeding time	Bone marrow depression Monitoring essential for first 12 weeks. Superior to aspirin for chronic peripheral arterial disease
Clopidogrel	75 mg od	Blocking of P2 TAC receptors on platelets	No adverse effects of ticlopidine, more rapid onset of action.
Dipyridamole	50 mg tds before food	Phosphodiesterase inhibitor. Also inhibits uptake of adenosine	Postural hypotension, headache, dizziness, nausea. More effective, if combined with aspirin or warfarin for prophylaxis in pts. with prosthetic heart valves
GPIIb/GPIIIa antagonists Abciximab	0.25 mg/kg bolus iv followed by 0.0125 µg/min (max 10 µg/min) infusion for 12 hrs	Decrease thrombus formation and risk of vaso-occlusion at the site of PCI	Increased risk of mucocutaneous and procedure related bleeding. Thrombocytopenia
Eptifibatide	180 µg/kg iv bolus x 2 10 min apart, followed by 2 mg/kg/min infusion for 18-24 hrs.	Can be give intracoronary safely and effectively for reduction of infarct size in MI	
Prasugrel	5-10 mg/d	Action similar to Clopidogrel	
Ticagrelor	90 mg/bd	Not a prodrug	Causes stronger platelet inhibition
		Faster onset of action	Reversible, which may be an advantage in reducing bleeding
Cangreolar	IV bolus of 30 µg/kg followed by an infusion of 4 µg/kg/min for at least 2 hrs	Reversible inhibitor of P2Y12	No serious bleeding effect
Vorapaxar	—	Orally active inhibitor of protease -activated receptor 1 (PAR- 1)	Increased intracranial bleeding

14. THE SPLEEN

FUNCTIONS OF THE SPLEEN

1. *Phagocytosis and sequestration* – Effect or damaged cells, antibody-coated cells and micro-organisms are removed by phagocytic cells in capillaries and sinuses. Reticulocytes are sequestered in the spleen for first 2-3 days following their release from the bone marrow, and red cell inclusions, such as Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured haemoglobin), siderotic granules (iron) and malaria parasites are removed from red cells.
2. *Immunological functions* – The spleen has an important role in the generation of an IgM response following antigen exposure, particularly polysaccharide antigens. It is also the source of opsonin 'tuftsin', a tetrapeptide that promotes neutrophil phagocytosis.
3. *Pooling of red cells and platelets* – Platelets (20-40%) and red cells (about 5%).
4. *Extramedullary haemopoiesis* – The spleen is a major haemopoietic organ in early foetal life. It retains the potential to support haemopoiesis in later life, reverting to an active haemopoietic organ in presence of bone marrow fibrosis (myelofibrosis) or erythroid hyperplasia (autoimmune haemolytic anaemia or thalassemia).

Causes of splenomegaly are listed in Table 46.

Table 46: Causes of splenomegaly.

Infections
• *Bacterial* – Septicaemia, typhoid, infective endocarditis, tuberculosis, syphilis, brucellosis.
• *Viral* – Hepatitis, infectious mononucleosis.
• *Protozoal* – Malaria, kala-azar, trypanosomiasis.
• *Rickettsial* – Typhus.
• *Fungal* – Histoplasmosis.
• *Parasitic* – Hydatid, bilharziasis.
Circulatory
• Congestive heart failure.
• Portal hypertension.
• Hepatic or portal vein thrombosis.
• Splenic vein obstruction.
• Splenic artery aneurysm.
Haematological
• *Haemolytic disorders* – Hereditary spherocytosis, elliptocytosis, warm-antibody AHA, pyruvic kinase deficiency, thalassemia, haemoglobinopathies (some), paroxysmal nocturnal haemoglobinuria.
• *Haematological malignancy* – Acute leukaemia, chronic myeloid leukaemia, chronic lymphoid leukaemia and lymphomas.
• *Myeloproliferative disorders* – Polycythemia vera, primary myeloid metaplasia.
Inflammatory and collagen disorders
• Acute rheumatic fever
• Felty's syndrome
• Systemic lupus erythematosus.
Granulomatous disorders
• Sarcoidosis
• Berylliosis
Metabolic storage diseases
Gaucher's disease, Niemann-Pick disease, Hurler's syndrome, histiocytosis X.
Splenomegaly of unknown ethology
Tropical splenomegaly, non-tropical splenomegaly.
Miscellaneous –Iron deficiency anaemia, pernicious anaemia, amyloidosis, myeloma, mastocytosis, splenic cysts, primary and secondary tumors, thyrotoxicosis.

CLINICO-PATHOLOGICAL FEATURES OF SPLENIC DISEASE

I. **Local effects** due to moderate to massive enlargement such as abdominal discomfort, dyspepsia, and symptoms due to pressure on bladder or colon.

II. **General effects**

1. *Hypersplenism* – The syndrome is diagnosed when the following are found together in absence of immature cells in peripheral blood – (a) Detectable splenomegaly, (b) anaemia, leucopenia or thrombocytopenia, (c) normal or hypercellular bone marrow. Several different mechanisms may be responsible in an individual patient.
2. *Red cell destruction* – in conditions characterised by specific abnormality of red cell viz. hereditary spherocytosis, haemolytic crisis of hereditary elliptocytosis and warm-antibody type of autoimmune haemolytic disease. Lesser degrees of red cell destruction occurs when there is marked splenic enlargement.
3. *Red cell pooling* – occurs in most enlarged spleens and is a drain on red cell volume from functional circulation of blood.

4. *Hypervolemia* – Marked splenomegaly leads to hyperkinetic portal hypertension produced by high blood flow through the enlarged spleen.
5. *Thrombocytopenia* – In about 80% cases of chronic ITP there is excessive platelet destruction predominantly in the spleen. It may also occur in chronic lymphocytic leukaemia and SLE.
6. *Leucopenia* – Leucopenia, and especially neutropenia, is commonly found in conditions where there is a splenomegaly, such as Felty's syndrome.

INVESTIGATION OF A CASE OF SPLENOMEGALY (OR HEPATOSPLENOMEGALY)

History

1. *Age* – Childhood cirrhosis between ages of 1 and 3 years.
2. *Sex* – Haemochromatosis more common in males.
3. *Family history* – in hereditary spherocytosis, haemochromatosis, Gaucher's disease.
4. *Personal history* – as regards diet, alcoholic intake.
5. *Past history* – of fever with rigors in malaria, history of jaundice and gastrointestinal bleeding.
6. *Fever* – Infections like malaria, kala-azar, typhoid, miliary tuberculosis, subacute infective endocarditis, brucellosis, etc. Leukaemia, lymphomas, disseminated lupus, sarcoidosis.
7. *Pruritus* – polycythemia (especially after a bath).
8. *Haemorrhages* – with extreme weakness in leukaemia.
9. *Pallor* – in leukaemia, haemolytic diseases.
10. *Bone pain* – Multiple myeloma, Gaucher's disease.
11. *Haematemesis* – may suggest cirrhosis.

Physical Examination

1. *Degree of splenomegaly*
   a. *Large to huge* – Chronic myeloid leukaemia, hairy cell leukaemia, lymphocytic lymphoma, malaria, kala-azar, bilharziasis, myelofibrosis.
   b. *Moderate* – All above plus Hodgkin's disease, leukaemias, polycythemia, portal hypertension, chronic haemolytic anaemia, tuberculosis, storage diseases.
   c. *Slight* – All above causes, acute and subacute infections, plus other causes of splenomegaly.
2. *Generalized lymphadenopathy* – Lymphoma, leukaemia, mononucleosis, generalised tuberculosis, endocarditis, brucellosis, Felty's syndrome, kala-azar in children, sarcoidosis.
3. *Palpable liver* – Malaria, kala-azar, leukaemia, infective hepatitis, portal hypertension, subacute infective endocarditis, tuberculosis, sarcoidosis, Hodgkin's disease, syphilis, severe haemolytic anaemias, congestive splenomegaly, reticulosis, myeloid metaplasia, amyloidosis, lipoid storage diseases, bilharziasis.
4. *Pallor and icterus* – Haemolytic anaemias, cirrhosis of liver.
5. *Petechiae and ecchymoses* – Acute leukaemia, terminal stage of chronic leukaemia, leucosarcoma with bone marrow metastasis, subacute bacterial endocarditis, SLE.
6. *Plethoric appearance* – Polycythemia vera.
7. *Pigmentation* – Grey-brown pigmentation best seen on medial and flexor aspects of the arms in hemochromatosis.
8. *Arterial spiders and palmar erythema* – in cirrhosis.
9. *Tremors* – in Wilson's disease and neurological complications of cirrhosis.
10. *Pinguecula* – in Gaucher's disease.
11. *Kayser-Fleischer ring* – at the periphery of the cornea in Wilson's disease.
12. *Bone changes* – Gaucher's disease, myelofibrosis, multiple myeloma, amyloidosis, metastatic carcinoma.
13. *Isolated splenomegaly* – Malaria, non-specific hyperplasia, primary splenic neoplasms, Gaucher's disease, sarcoid.

Investigations

1. ***Blood Picture and Blood Tests***
   a. *Leucopenia* – Typhoid, malaria, kala-azar, syphilis, tuberculosis, sarcoid, portal hypertension, nonspecific hyperplasia, neoplasm of spleen such as primary lymphosarcoma, haemangioma or cyst; rheumatoid arthritis (Felty's syndrome).
   b. *Leucocytosis* – Pyogenic infections, infectious mononucleosis, leukaemias, polycythemia, most haemolytic anaemias.
   c. *Lymphocytosis* – Infectious mononucleosis, brucellosis, tuberculosis.
   d. *Pancytosis* – Polycythemia.
   e. *Reticulocytosis* – Haemolytic anaemia.
   f. *Thrombocytopenia* – Leukaemia or other malignancy.
   g. *Blood smear* – for diagnosis of malaria, leukaemia, polycythemia, infectious mononucleosis, hereditary spherocytosis.

h. *Blood culture* – in subacute infective endocarditis.

i. *Special tests* – (a) Serum bilirubin – in haemolytic anaemias. (b) Standard agglutination test – for brucellosis. (c) Blood test – for syphilis. (d) Paul-Bunnell test – for infectious mononucleosis. (e) Tests for abnormal haemoglobins, and Coomb's test in thalassemias (Cooley's anaemia). (f) Rectal biopsy or aspiration of subcutaneous fat from anterior abdominal wall for systemic amyloidosis. (g) Serum iron – raised in haemochromatosis. (h) Serum copper – low levels in Wilson's disease. (i) Auto antibodies – ANA, Anti-ds-DNA, Anti-sm in SLE.

2. ***Radiology*** – (a) *Plain film of abdomen* – for detecting splenic enlargement. Enlargement may also produce a raised left hemi-diaphragm, and displace adjacent organs in a barium meal or barium enema film or IV urogram. (b) *Chest* – for miliary tuberculosis, sarcoidosis, Hodgkin's disease and histoplasmosis. (c) *Bones* – Expansion of lower ends of long bones especially femur in Gaucher's disease, increased density in myeloid metaplasia, and 'hair-on-end' or 'brush' appearance of skull in thalassemia.
3. ***Radioisotopic Spleen Scanning*** – Techniques include 99 Tc-colloid liver-spleen scan, computed tomography and ultrasound scanning of the left upper quadrant. Utility – (a) Detects enlargement of spleen. (b) It can indicate focal lesions, infarcts, splenic rupture, accessory spleen and absence or hypoplasia of the spleen. (c) Sequential estimates of organ radioactivity after injection of chromium 51-labelled autologous red cells gives estimate of red cell pooling and destruction in haemolytic anaemias. If splenic destruction is significantly greater than the apparent red cell loss in the liver, it provides supportive evidence for value of splenectomy. (d) Similar studies with isotope-labelled platelets can be used in thrombocytopenic states.
4. ***Liver biopsy*** – Sarcoidosis, collagen disease, Hodgkin's disease, amyloid disease, haemochromatosis, histoplasmosis.
5. ***Bone marrow examination*** –Haematological malignancy including leukaemia, myeloproliferative disorders, lymphoma, myeloma, kala-azar.
6. ***Lymph node biopsy*** – of value in tuberculosis, Hodgkin's disease, sarcoid and histoplasmosis.
7. ***Skin tests*** – Tuberculin test – -ve in sarcoidosis.
8. ***Tests for portal hypertension*** – Refer.
9. ***Serum proteins*** – Elevated globulin with reversed albumin globulin ratio in multiple myeloma, cirrhosis of liver and occasionally lymphosarcomatosis and disseminated lupus.
10. ***ESR AND LDH*** – commonly elevated in lymphoma.
11. ***Splenectomy*** – as a diagnostic measure in the presence of obscure anaemia with leucopenia and thrombocytopenia with splenomegaly.

Differential Diagnosis of Chronic Splenomegaly

1. ***Cirrhosis of liver***
   a. Symptoms and signs of hepatocellular failure – Spider naevi, liver palms, alopecia, gynecomastia and testicular atrophy in males, icterus, foetor hepaticus. Palpable enlarged liver.
   b. Evidence of portal hypertension – Ascites, prominent veins on abdomen, haematemesis, piles.
   c. Diagnosis by liver biopsy, demonstration of oesophageal varices by barium swallow, laparoscopy and scanning.
2. ***Infections, subacute and chronic***
   a. *Chronic malaria*
      - History of fever with rigors with classical features of the attack – cold stage, hot stage, sweating stage.
      - Spleen very large and firm.
      - Liver may be enlarged.
      - Severe anaemia.
      - Malarial parasites in peripheral blood or sternal marrow.
      - Leucopenia.
      - Therapeutic test with adequate dose of antimalarial drug during fever.

   b. *Kala-azar*
      - Residence in endemic area.
      - Splenomegaly – which may be massive.
      - Recurrent fever – Double rise of temperature in 24 hours may be seen.
      - Liver enlarged but not grossly like spleen.
      - Anaemia.
      - Loss of hair and pigmentation of skin.
      - Generalized lymphadenopathy – especially in children. Nodes are soft, non-tender.
      - Other features – Cough, haemorrhagic features (notably epistaxis).
      - LD bodies – on stained material from bone marrow or splenic aspirate.

c. *Subacute infective endocarditis*
- Unexplained fever.
- Presence of cardiac murmur.
- Presence of petechiae, anaemia, peripheral emboli; clubbing of fingers.
- Red cells in urine.
- Positive blood culture.

d. *Brucellosis*
- History of ingestion of raw milk, or occupation hazard in veterinary surgeons, laboratory personnel or slaughter house workers.
- Patient not toxic in spite of high fever.
- Spleen of moderate size, rarely massive.
- Liver may be enlarged particularly, if spleen is very large.
- Back pain common.
- Culture of organism from blood or bone marrow. Complement fixation and anti-human globulin tests in chronic infection.

e. *Tuberculous splenomegaly* - In rare cases tuberculous enlargement of spleen occurs with little involvement of other organs. Blood picture shows anaemia, leucopenia, or thrombocytopenia, either singly or in combination. Weakness, lassitude, loss of weight and often pyrexia. Bleeding may occur. X-ray of spleen may demonstrate areas of calcification.

f. *Bilharziasis* (Egyptian splenomegaly) – (i) History of residence in endemic area. (ii) Preceding toxic stage with urticaria, fever, diarrhoea. (iii) Emaciation. (iv) Hepatomegaly and progressive splenomegaly. (v) Dilatation of abdominal veins. (vi) Ascites in terminal stages. (vii) Ova in stools and positive complement deviation test. (viii) Aspiration liver biopsy will show evidence of cirrhosis and causative ova.

3. ***Myeloproliferative disorders***

a. *Chronic myeloid leukaemia (Chronic phase)*
- Fatigue, weight loss, sweating, anaemia.
- Haemorrhages – easy bruising, ecchymoses.
- Splenomegaly with or without hepatomegaly.
- Blood findings – Raised white cell count (30-400 $\times$ 10^9/1). Differential shows granulocytes at all stages of development. Blast cells.

b. *Polycythemia vera* (PV)
- Most patients over 40 years of age.
- Symptoms due to hyper-viscosity – a. Mild headache. b. Neurological disturbance –Ataxia, vertigo, confusion. c. Visual disturbance – Blurring of vision, dilatation and segmentation of retinal veins, 'sausage' appearance of retinal veins.
- Symptoms due to haemorrhages – Epistaxis, gastro-intestinal or genitourinary bleeding.
- Palpable splenomegaly, raised haematocrit. Bone marrow – Hyperplasia of all marrow elements and large megakaryocytes with hyperlobulated nuclei.

c. *Myelofibrosis*
- Generalized symptoms of marked lassitude, loss of weight and night sweats.
- Splenomegaly may be massive, pain due to splenic infarct.
- Anaemia with leucoerythroblastic blood picture. Erythrocytes show characteristic tear drop poikilocytes.
- Neutrophil alkaline phosphatase score elevated (Normal 40-100)
- Bone marrow – difficult to aspirate. Trephine biopsy shows increased number of megakaryocytes and increased reticulin and fibrous tissue replacement.
- X-ray – Ground glass appearance of bones of axial skeleton.

d. *Primary thrombocythemia*
- Bleeding – from GI tract or spontaneous bleeding after minor trauma resulting in large haematomas. Purpura rare.
- Gross splenomegaly does not occur.
- Very high peripheral platelet count and increased number of megakaryocytes in bone marrow.

4. ***Lymphoproliferative disorders***–

a. *Chronic lymphocytic leukaemia*
- Mostly in second half of life and more in males.
- Lymphadenopathy, infiltration of salivary glands, infiltration of serous membranes resulting in pleural or pericardial effusion, skin infiltration with nodules.
- Peripheral lymphocytosis and increase in mature lymphocytes in bone marrow.

b. *Hodgkin's disease*
- Most often in young adults.
- Localized, painless lymphadenopathy – in neck, axilla or inguinal region in decreasing order of frequency.
- Occasionally involvement of mediastinal nodes, spleen, liver and extralymphatic deposits in skin may be presenting symptom. Pruritus.
- Systemic symptoms – Fever, sweating, weight loss.
- Diagnosis – Presence of Reed-Sternberg cells in gland biopsy.

c. *Non-Hodgkin's lymphoma*
- Low grade and large cell lymphomas predominantly in elderly.
- Painless peripheral lymphadenopathy.
- Symptoms related to vascular occlusion – Cerebral, coronary, splanchnic and deep veins.
- Weight loss, fever, night sweats.
- Hepatosplenomegaly
- Clinical features due to involvement of unusual sites, e.g. skin (Sezary's syndrome/mycosis fungoides), tonsils and adenoids, salivary glands, GI tract, lungs, CNS (HIV-related and lymphoblastic), jaw (Burkitt's lymphoma) and testis.
- Detection of immunological markers on circulating lymphoma cells or fixed tissue from lymph nodes or other sites.

6. ***Anaemias***

a. *Chronic haemolytic anaemia*
- Anaemia varies from time to time but develops rapidly with haemolytic crises.
- Jaundice usually mild and of lemon yellow tint.
- Features of chronic cholecystitis due to pigment gallstones.
- Ulcers of the legs and pigmentation from old ulcers, usually over the malleoli may be seen.
- Evidence of haemolysis in blood –Reticulocytosis and upto 1 normoblasts per 100 leucocytes.

b. *Iron deficiency anaemia*
- Mild degree of splenomegaly with hepatomegaly.
- Nail changes – Platynychia and koilonychia.
- Smooth and pale tongue.
- Associated condition, e.g. bleeding piles, hookworm infection, menorrhagia, etc.
- Decreased red cell count, haemoglobin and haematocrit with hypochromia in peripheral smear.

c. *Megaloblastic anaemia*
- Diarrhoea, loss of appetite and weight.
- Mild jaundice may give the patient a lemon yellow tint.
- Glossitis and angular cheilosis.
- Liver usually not enlarged.
- Macrocytosis with MCV usually above 100 femtolitres. Bone marrow – Megaloblastic erythropoiesis.

7. ***Multiple myeloma***
- Middle-aged or elderly.
- Bone pain – commonest symptom involving thoracic and lumbar spine.
- Generalized osteoporosis common.
- Anaemia.
- Kidney failure.
- Recurrent infection.
- Diagnosis – (a) Plasmocytosis on bone marrow aspiration. (b) Monoclonal globulin spike on serum or urine electrophoresis. (c) Well-defined lytic bone lesions.

8. ***Collagen diseases***

a. *Systemic lupus erythematosus*
- Mostly in women.
- Multisystem disease with fever, arthritis, skin and renal involvement.
- Lymphadenopathy.
- Hepatic enlargement.
- LE cells in peripheral blood or bone marrow.

b. *Felty's syndrome* – Chronic splenomegaly, neutropenia, with chronic rheumatoid arthritis in adults. Other features which may be observed are weight loss, pigmentation of skin, hepatomegaly, moderate lymph node enlargement and ulceration of the leg.

9. ***Tropical splenomegaly syndrome*** **(TSS)**

- Gross splenomegaly in immune adults from areas of endemic malaria.
- High serum IgM.
- Moderate hepatomegaly.
- Hepatic sinusoidal lymphocytosis.
- Regression of above features with antimalarial treatment and prolonged prophylaxis.

10. ***Sarcoidosis***
    - Lymphadenopathy hilar and elsewhere
    - Extrathoracic sarcoidosis – Skin, CNS, bone, heart
    - Splenomegaly
    - Hypercalcemia
    - Diagnosis by biopsy of lymph node, chest radiograph
11. ***Amyloidosis*** Primary (AL), Secondary (AA)
    - Nephrotic syndrome, renal impairment
    - Cardiac – Restrictive cardiomyopathy, dysrhythmia
    - Macroglossia
    - Hepatosplenomegaly
    - Diagnosis: Biopsy of rectal mucosa or abdominal fat.
    - Bence-Jones proteins in urine
12. ***Lipoid granulomatosis*** **(Table 47)**

In children

a. *Congenital syphilis* – Spleen usually enlarged two fingers breadth below the costal margin, smooth and firm. Dermal and visceral manifestations of syphilis. Positive tests for syphilis.

b. *Infantile childhood cirrhosis* – Predominantly in boys aged 1-3 years. Progressive hepatic failure with hepatomegaly, splenomegaly, jaundice and ascites.

c. *Thalassemia major* – (i) Mongoloid facies. (ii) Splenomegaly usually marked, moderate to marked hepatomegaly. (iii) Periodic attacks of fever common. (iv) Blood – Target or oval cells, many normoblasts. (v) X-ray skull – Thickening of diploe, thinning of inner and outer tables with perpendicular striations between the two layers – "hair standing on end" appearance.

d. *Still's disease* – Rheumatoid type of arthritis, splenomegaly, fever and anaemia, lymphadenopathy and leucocytosis.

e. *Hurler's syndrome* – Dwarfism, hepatosplenomegaly, coarse facies, corneal clouding, joint contractures, mental retardation, umbilical hernia, hirsutism, macroglossia, thoracolumbar kyphosis.

Splenectomy: Indications in haematological disorders-

Table 47: Lipoid granulomatosis.

	Gaucher's disease	*Niemann-Pick's disease*	*Hand-Christian disease*
Familial predisposition	Frequent	None	None
Age	Onset in childhood	Infancy	Early childhood
Spleen	Marked splenomegaly	Moderate splenomegaly	Slight to moderate splenomegaly
Other features	Chronic progressive anaemia	Slight or no anaemia	Diabetes insipidus
	Leucopenia	Leucocytosis	Exophthalmos
	Hemorrhages	Gastro-intestinal disorders	Defects in membrane bones
	Cortical thinning of long bones	Retarded development	Retarded development
	Skin and conjunctival pigmentation	Brown skin pigmentation	
Course and Prognosis	Chronic course	Short course. Fatal within 2 years	Slow course. Fatal in 50%

A. **Diagnostic** – Splenomegaly is occasionally an isolated finding and the cause may not be identified despite investigations, e.g., simple cyst or haemangioma, chronic granulomas, plasmocytoma and in some atypical cases of lymphoproliferative disorders. In such cases splenectomy may be justified for diagnostic reasons. The fact that the spleen is of normal size does not exclude possibility of the organ being affected by lymphoma.

B. **Therapeutic**

1. *Rupture of the spleen* – With a normal spleen severe trauma is required to cause rupture. The diseased spleen may rupture with trivial trauma, e.g., in infectious mononucleosis, acute and chronic leukaemias, myelomatosis, autoimmune haemolytic disease and congestive splenomegaly.
2. *Local effects of splenic enlargement* – such as discomfort due to massive splenomegaly, dyspepsia, recurrent infarction, perisplenitis.
3. *Correlation of cytopenias* – (a) *Absolute indications* – (i) Hereditary spherocytosis and haemolytic variant of hereditary elliptocytosis. (ii) Chronic idiopathic thrombocytopenic purpura. Even if platelet count does not return to normal, it may be possible to lower the dose of steroids. (iii) Primary hyper-

splenism – non-tropical variety for correction of cell deficits and to exclude other diagnoses requiring additional therapy. (b) *Relative indications* – (i) Warm-antibody autoimmune haemolytic disease when IgG or IgA antibodies are attached to the red cells. (ii) To relieve cytopenias resulting from red cell and platelet pooling, haemolysis and platelet destruction in cases with moderate to massive splenomegaly, e.g., chronic lymphocytic or granulocytic leukaemia, Gaucher's disease. (c) *Doubtful outcome but severe* (at times life-threatening) *condition* – Thrombotic thrombocytopenic purpura, pyruvic kinase deficiency, some cases of PNH, and the improvement of the effect of platelet transfusions in aplastic anaemia.

Hypersplenism: A peripheral blood cytopenia which is cured by splenectomy. It is due to pooling of cells within the spleen and rapid destruction of cells within the spleen.

Diagnosis

1. Splenomegaly.
2. Peripheral blood cytopenia.
3. Normal or hypercellular marrow.
4. Demonstration of shortened red cell survival.

Treatment: Splenectomy, if causative underlying disorder cannot be corrected, e.g. lymphomas, β-cell hairy cell leukaemia. Felty's syndrome, Gaucher's disease.

Hyposplenism – indicates diminished or absent splenic function.

Causes

- Splenectomy
- Splenic agenesis
- Splenic atrophy and functional hyposplenism and bone marrow transplantation
- Sickle cell disease
- Splenic irradiation
- Essential thrombocythemia
- Adult coeliac disease and dermatitis herpetiformis
- Ulcerative colitis
- Crohn's disease
- Systemic lupus erythematosus
- Infiltration (lymphoma, amyloid)

Haematological Changes

Red cells: Presence of Howell-Jolly bodies, and other red cell inclusion acanthocytes and target cells.

White cells: Neutrophil leucocytosis, which settles within few weeks. Modest lympho and monocytosis persist indefinitely.

Platelets: Count rises immediately after splenectomy, usually peaking at 7-12 days and returning to normal within 2 months.

Post-splenectomy sepsis: Rapid onset and fulminant course, associated with multiple organ failure and DIC. Risk of infection persists throughout life, but is greatest in those under 5 years of age, in those splenectomised for malignant disease. Most are due to Strep. pneumoniae, others are H. influenzae and N. meningitidis, malaria, babesiosis.

15. BONE MARROW TRANSPLANTATION

Transplantation is the reconstitution of the full hemopoietic system by transfer of the pluripotent cells present in the bone marrow (stem cells). This usually requires prior ablation of patient's own marrow by intensive chemotherapy or chemoradiotherapy.

TYPES OF TRANSPLANTATION

1. ***Allogenic transplantation***– is when another individual acts as the donor – usually a sibling of the patient, sometimes a normal volunteer. All cases, however, require a full or near HLA match – that is they should be HLA compatible.

Indications

When it is the sole chance of cure:

- Primary immunodeficiency syndrome
- Aplastic anemia
- Thalassemia
- Myelodysplasia
- Multiple myeloma
- Sickle cell disease
- Inborn errors of metabolism
- Chronic myeloid leukaemia

When it is probably better than conventional treatment:

- AML (first or second complete remission)
- ALL (first or second full remission)
- In children in whom ALL is the commonest leukaemia, most will be cured by standard chemotherapy alone, and transplantation is only reserved for relapse.

2. ***Autologous transplantation***– is when patient acts as his or her own source of stem cells.

Probable benefit
Relapsed Hodgkin's lymphoma
ALL (first or second complete remission)
Relapsed testicular cancer

Possible benefit
CML
Disseminate breast cancer
Disseminate lung cancers
Other solid tumors
Severe autoimmune disease

Proved benefit
Relapsed non-Hodgkin's lymphoma (intermediate and high grade)
AML (first or second complete remission), Multiple myeloma.

Complications

Early complications of transplants

Chemoradiotherapy

- Nausea and vomiting
- Reversible alopecia
- Fatigue
- Dry, inflamed skin
- Mucositis
- Veno-occlusive disease

Infections

- Bacterial (Gram -ve and +ve)
- Viral-Herpes zoster virus, cytomegalovirus (particularly pneumonitis)
- Fungal – Candida, aspergillus
- Atypical organisms – Pneumocystis pneumonia, toxoplasma, mycoplasma, legionella

Acute graft versus host disease (allograft only)

- Rash
- Diarrhoea
- Jaundice

Graft versus host disease – is an immune reaction between donor and recipient. It is mediated by T cells in the graft, which recognise and attack antigens in the host tissue. Acute GVHD develops within 3 months post-transplantation. Chronic GVHD develops in transplant patients **between 3 months to 2 years.**

Clinical Features

Acute

- Erythematous, maculopapular rash
- Liver disease
- Profuse diarrhoea
- Jaundice

Chronic

- Sclerotic atrophic skin
- Sicca syndrome
- Mucosal ulceration
- Malabsorption syndrome
- Recurrent chest infections
- Cholestatic jaundice
- Joint movement restriction
- Hyposplenic infections
- Myelosuppression

Late complications of transplantation

- Relapse of the original underlying disease
- Infertility (both sexes)
- Hypothyroidism
- Secondary malignancy
- Late sepsis due to hyposplenism
- Cataracts (secondary to total body irradiation)
- Psychological disturbance

16. THE BLOOD IN SYSTEMIC DISEASE

ANEMIA OF CHRONIC DISORDERS

Mechanism

- Slightly shortened RBC survival
- Improved bone marrow response to anemia
- Increased synthesis of ferritin (and other acute phase proteins)
- Defective transfer to iron from reticuloendothelial stores to RBC precursors
- Impaired transferrin production

Pathogenesis. ACD is characterized by:

- Relatively low erythropoietin level
- Reduced RBC survival as a result of phagocytosis by macrophages
- Reduced intestinal iron absorption
- Retention of iron in macrophages

Malignant Disease

Anemia often results from anemia of chronic disorders, and is commonly associated with raised ESR. Anemia can be due to loss of blood in patients with GI malignancy.

Reactive bone marrow may lead to leucocytosis and/or thrombocytosis. In extreme cases (usually associated with necrotic tumors or widespread malignancy), the leucocytosis may mimic CML.

Bone marrow infiltration typically gives a leucoerythroblastic blood picture. This appearance is nonspecific and occurs in various conditions that infiltrate the bone marrow.

Haemostatic failure may be caused by microangiopathic hemolytic anemia (typically associated with mucin-secreting adenocarcinomas) or DIC (particularly prostate carcinoma).

Infection

Bacterial infections – (a) *Disseminated TB* can produce features that mimic disseminated malignancy and myeloproliferative disorders. (b) *Clostridium welchii.* Severe infections may be associated with acute haemolysis.

Viral infections – (a) Symptomatic thrombocytopenia occurs occasionally in patients with rubella, infectious mononucleosis or varicella-zoster virus. (b) In viral haemorrhagic fevers, haemorrhagic features vary from mild thrombocytopenia to severe bleeding tendency.

Parasitic disease – (a) Eosinophilia in helminthic infections. (b) Anemia in hookworm disease. (c) Malaria is associated with anemia with a complex pathophysiology.

Autoimmune disease Autoimmune phenomena seen in RA, SLE, giant cell arteritis, scleroderma, ankylosing spondylitis and polyarteritis nodosa, include hemolytic anemia, thrombocytopenia and leucopenia.

Renal disease Kidney failure is commonly associated with anemia that principally results from lack of erythropoietin production. Uraemia adversely affects platelet function and may lead to a bleeding diathesis. Occasionally erythrocytosis or polycythemia is caused by an erythropoietin secreting kidney tumour.

GI disease Anemia secondary to GI blood loss, and effects of malabsorption. Inflammatory bowel disease may be associated with anemia of chronic disorders.

Liver disease Anemia has some features of anemia of chronic disorders. Anemia may be macrocytic and target cells may be seen in the blood. Thrombocytopenia is common. Haemorrhagic diathesis due to impaired synthesis of clotting factors.

Endocrine disorders RBC mass is increased in hyperthyroidism and decreased in hypothyroidism, reflecting the requirements for oxygen delivery. Hypothyroidism is commonly associated with macrocytosis. Anemia in hypopituitarism.

Cardiac disorders Cyanosis and polycythemia in children with congenital heart disease. In severe cases, polycythemia may be associated with thrombotic episodes or other haemostatic abnormalities, suggesting a degree of intravascular consumption. Low grade haemolysis is sometimes seen in patients with severe aortic disease, and less often in mitral stenosis. It probably results from abnormally turbulent flow, which is more commonly seen following mechanical valve replacement.

Respiratory disorders Neutrophil leucocytosis in bacterial infection, e.g. pneumonia. Secondary polycythemia in COPD. Mycoplasma pneumonia is associated with circulating cold agglutinins in 75%. Pulmonary eosinophilia is a group of conditions in which eosinophil count is raised together with pulmonary infiltrates.

CHAPTER

6

Endocrine Disorders

1. PITUITARY GLAND

Most patients with functioning adenomas present with signs and symptoms related to hormonal hypersecretion including:

- Acromegaly (via the action of GH and insulin-like growth factor I—IGF-I)
- Cushing's disease (via the action of ACTH and cortisol)

Amenorrhoea-galactorrhoea syndrome (via the action of prolactin and subsequent suppression of the pituitary gonadotropins).

ACROMEGALY

Acromegaly is a clinical condition resulting from prolonged excessive circulating levels of growth hormone (GH) in adults. Acromegalic gigantism results from acromegaly in young individuals before epiphyseal fusion. Causes of acromegaly are given in Table 1.

Clinical Features

1. ***Local space-occupying effects***:
   (a) *Inside pituitary fossa*: Bitemporal loss of vision due to compression of visual pathways.
   (b) *Outside pituitary fossa*:
   - Diplopia (cranial nerve palsies with extraocular muscle dysfunction).
   - Papilloedema due to upward growth and obstruction of CSF flow into third ventricle.
   - Personality changes, focal hemispherical neurological signs and epilepsy (growth into frontal and temporal lobes).

Table 1: Causes of acromegaly

1. Pituitary adenoma (95%)
2. Excessive secretion of GH releasing hormone (GHRH) from carcinoid tumors (particularly bronchial), pancreatic islet cell or adrenal tumours.
3. Ectopic GH-secreting pancreatic islet cell tumours.
4. As part of multiple endocrine neoplasia type 1.

2. ***Due to GH excess*** (Table 2)

Table 2: Clinical features due to GH excess

(a) *General*
– Fatigue – Weight gain – Heat intolerance – Increased sweating
(b) *Skeletal changes*
– Enlargement of hands and feet, spade like hands. – Enlargement of supraorbital ridges. – Enlargement of facial bones and prognathism. – Spacing apart of teeth. – Clavicles thickened. – Changes in spine—osteoporosis, kyphosis, lordosis and scoliosis. – Carpal tunnel syndrome.
(c) *Skin and subcutaneous tissues* – Tongue enlarged with difficulty in articulation. – Thickening of lips and nose. – Skin coarse and greasy. – Thickening of soft tissues of hands and feet. – Hypertrophy of muscular system in initial stages. – Mammary hyperplasia. – Hypertrichosis.
(d) *Cardiovascular*
– Hypertension, – Cardiac failure or acromegalic cardiomyopathy, – Coronary artery disease – Arrhythmias.
(e) *Respiratory*
– Deep voice due to enlargement of larynx. – Lungs enlarge proportionately with thorax.
(f) *Metabolic*: Impaired glucose tolerance in about 25%.
(g) *Malignancy*: Prevalence of malignant disease (particularly colonic cancer) is probably increased.

3. ***Effects of pituitary tumor***

   (a) Headaches. (b) Upward extension of the tumor may occasionally cause compression of IIIrd, IVth or VIth cranial nerves. (c) Related to other hormones (i) Hyperprolactinaemia is common. Women may present with amenorrhoea and galactorrhoea or infertility, and men with low libido and impotence. (ii) Hypopituitarism occurs unless the tumour is small. Loss of anterior pituitary hormone secretion is seen as early failure of luteinizing hormone and, much later, thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH). Hypothyroidism and hypoadrenalism occur as a result of decreased secretion of TSH and ACTH.

4. ***Related to other hormones***

   (a) *Galactorrhoea*, due to (i) Concomitant adenomatous secretion (in 30%). (ii) Compression of posterior pituitary stalk by adenoma causing reduced ingress of prolactin-inhibitory factor (PIF). (c) Reduced pituitary TSH secretion leading to compensatory elevation of hypothalamic TR secretion with resulting stimulation of prolactin release.

   (b) *Polydipsia* due to (i) Osmotic diuresis due to glucose intolerance. (ii) Diabetes insipidus. (iii) Dehydration secondary to hyperhidrosis.

   (c) *Variable deficiency of* GnRH (Gonadotrophic releasing hormone). ACTH (Adrenocorticotropic hormone). TSH (Thyroid stimulating hormone).

Investigations

A. ***Imaging***

1. *Radiography* – (a) Skull – (i) Enlarged sella turcica (in 90%). (ii) Enlarged frontal sinuses, increased skull thickness. (iii) Macrognathia, wide-spaced teeth (Fig. 1).

   (b) Fingers – 'Arrowhead' tufting of finger tips.

   (c) Heel-pad sign – Heel pad >23 mm thick may indicate acromegaly.

2. *CT scanning* – if pituitary fossa abnormal on plain radiograph. A large adenoma is easily detected in CT scans taken after IV contrast. Coronal scanning with high definition may show characteristic features of an intrasellar micro-adenoma.

3. *MRI* – Sagittal view is useful in identifying relationship between suprasellar and infrasellar structures. It is better than CT scanning in distinguishing optic pathway from suprasellar component of a tumor.

4. *Imaging of chest and abdomen* – in whom CT scanning or MRI does not reveal pituitary adenoma.

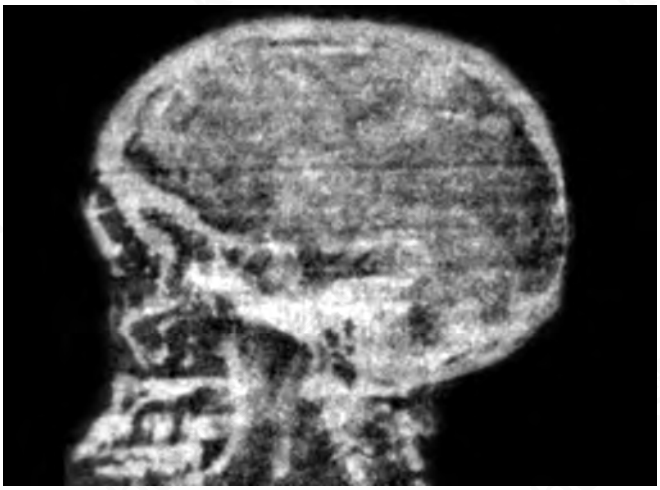


Fig. 1: Skull in acromegaly. Note enlargement of sella turcica and of frontal bones, generalized thickening of skull bones and prognathism. Other causes of enlarged sella – Primary hypothyroidism, pregnancy, empty sella syndrome (classically in obese hypertensive multipara)

B. ***Biochemical diagnosis*** – GH levels elevated but the degree of elevation does not correlate with any manifestation of the disease.

- *Glucose tolerance test* – is the accepted diagnostic method measuring glucose and GH. In healthy individuals, GH becomes undetectable during the test.
- *Insulin-like growth factor I (IGF-I) levels* – GH stimulates production of IGF-I predominantly in the liver; IGF-I levels can be determined to assess disease activity in acromegalics, reflecting overall GH secretion. Unlike GH, IGF-I levels do not fluctuate widely throughout the day.

Management

Treatment should aim to reduce GH levels to < 5 mU/liter

1. *Surgery* – by transphenoidal route is the first-line treatment in most pts; up to 90% microadenomas are cured.

2. *Radiotherapy* – is often advised if initial attempts at surgery do not reduce GH levels to 5 mU/1 (Implantation of radioactive isotope yttrium-90 into substance of pituitary gland). It causes a major reduction in GH levels during first 2 years. Hypopituitarism may occur.

3. *Medical therapy* – used principally as adjunct to ablative treatment of pituitary tumor.

   (a) Long-acting somatostatin analogues – Octreotide reduces GH levels to <5 mU/L in about 50% of patient. Dose: 100 µg t.d.s. can be increased up to 1500 µg/day. Long-acting injections have effects that persist for one month. Sandostatin - LAR is

a sustained-release, long-acting formulation of octreotide incorporated into microspheres that sustain drug levels for several weeks after intramuscular injection. GH suppression occurs for as long as 6 weeks after a 30-mg intramuscular injection; long-term monthly treatment sustains GH and IGF-I suppression and also reduces pituitary tumor size in 50% of patients. Lanreotide autogel, a slow-release depot somatostatin preparation, is a cyclic somatostatin octapeptide analogue that suppresses GH and IGF-I hypersecretion after a 60-mg subcutaneous injection Side-effects – Initiation of therapy may cause colicky abdominal pain and diarrhea. Gallstones are a long-term side effect in about 30% of patients.

(b) GH-receptor antagonist – Pegvisomant is administered s.c. as 40 mg/day dose followed by self-administration of 10 mg/day. Based on serum IGF-2 levels, the dose is titrated at 4–6 weeks intervals to maximum 40 mg/day. Liver function needs monitoring.

(c) Dopamine agonists - Bromocriptine and cabergoline may modestly suppress GH secretion in some patients. Very high doses are usually required to achieve modest GH therapeutic efficacy.

ADULT GROWTH HORMONE DEFICIENCY (AGHD)

Symptoms are nonspecific and include abdominal obesity, reduced strength and exercise capacity, impaired psychological well being, reduced vitality and mood disturbances.

CUSHING'S DISEASE

Cushing's disease results from basophilic adenoma of anterior pituitary. (see Cushing's syndrome).

PROLACTINOMA

Prolactin secretion is under tonic inhibitory control by hypothalamic dopamine, such that interruption of the pituitary stalk produces Hyperprolactinaemia. Clinical features of prolactinoma are listed in Table 3. Causes of hyperprolactinaemia are given in Table 4.

Investigations

- Serum thyroxine and TSH levels to exclude hypothyroidism
- Pituitary imaging preferably with MRI.

Table 3: Clinical features of prolactinoma

Caused by prolactin excess
Women • Oligomenorrhoea/amenorrhoea • Galactorrhoea • Infertility • Hirsutism/acne (less common) • Osteoporosis
Men • Reduced libido • Impotence • Oligospermia • Erectile dysfunction • Galactorrhoea (less common)
Caused by tumor mass (usually in men)
• Headache • Visual field defects (classically bitemporal hemianopia) • Cranial nerve palsies • Temporal lobe seizures • Unilateral exophthalmos (rare)
Caused by other pituitary hormone deficiency
• Microprolactinoma – Other pituitary functions usually normal • Macroprolactinoma – Varying degrees of hypopituitarism may be present

Table 4: Causes of hyperprolactinaemia

Physiological • Pregnancy • Lactation • Stress
Drugs • Anti-emetics (domperidone, prochlorperazine) • Phenothiazines (chlorpromazine, haloperidol) • Tricyclic antidepressants
Primary hypothyroidism
Pituitary tumors • Prolactinoma • GH secreting (raised prolactin in 30% of acromegalics)
Polycystic ovary syndrome
Uncommon hypothalamic/stalk lesions • Sarcoidosis • Langerhan's cell histiocytosis • Hypothalamic tumors
Chest wall stimulation • Repeated self-examination of breasts • Post-herpes zoster
Liver/kidney failure

- Dynamic testing with dopamine receptor antagonist (e.g. domperidone) when prolactin level is not greatly raised.
- Full assessment of pituitary function in patients with clinical or biochemical evidence of hypopituitarism or with a microadenoma.
- Urgent prolactin assay in all patients with visual failure and a large pituitary lesion.

Management

Indications for treatment – Infertility, menstrual disturbance with long-term hypogonadism (osteoporosis risk), troublesome galactorrhoea, enlarging pituitary tumor with pressure effects (particularly visual failure).

Drug therapy – Dopamine receptor agonists – Bromocriptine initially 1.25 mg at bed time, gradually increased to 2.5 mg t.d.s. Cabergoline and quinagolide are longer-acting and better tolerated than bromocriptine.

Surgery and radiotherapy – Patients who are intolerant of dopamine receptor antagonists or who fail to exhibit tumor shrinkage may require transphenoidal surgery and/or pituitary radiotherapy.

NELSON'S SYNDROME

Pituitary tumour develops after bilateral adrenalectomy for Cushing's disease in 10–15% of patients and is associated with markedly raised ACTH and β-lipotrophin levels. Diagnosis suspected from increasing skin and mucosal pigmentation.

PRECOCIOUS PUBERTY

In girls – Most often due to premature secretion of gonadotropins in excess of that appropriate to a person's age resulting in premature development of secondary sex characters and rapid skeletal growth. Treatment – Medroxyprogesterone (Provera) 100 mg of depot preparation every 2 weeks, later increased to 300 mg every 2 weeks.

In boys – Most often pathological lesion exists and must be looked for.

HYPOPITUITARISM

Juvenile onset – (a) Selective gonadotrophic failure – Normal or increased stature, eunuchoid habitus, gonadal and genital underdevelopment; amenorrhoea in females. (b) Selective growth hormone failure with dwarfism. (c) Panhypopituitarism.

Adult panhypopituitarism (Simmond's disease).

Causes – (a) Pituitary tumours. (b) Tumours in region of hypothalamus. (c) Granulomas – Tuberculosis, sarcoidosis, histiocytosis, syphilis. (d) Infarction – Post-partum necrosis (Sheehan's syndrome), pituitary apoplexy. (e) Unknown, especially isolated defect. (f) Miscellaneous – Haemochromatosis, trauma, maternal deprivation, after treatment of pituitary lesion.

Clinical Features

See Table 5 for the Clinical features of pituitary insufficiency.

Investigation: of Hypopituitarism

1. Visual fields – should be charted.
2. Imaging – (a) *Plain skull radiograph* – as initial screening procedure. Enlargement of pituitary fossa, undercutting of anterior clinoid processes and thinning of dorsal sella if large intrasellar tumour. A small pituitary adenoma initially enlarges on one side of the pituitary fossa, in a lateral film this may be seen as a 'double

Table 5: Clinical features of pituitary insufficiency

Deficient hormone	*Manifestations*
Growth hormone	Wrinkling of skin (crow's feet) Tiredness Lack of muscle bulk and strength
LH/FSH	*Women* Oligomenorrhoea/amenorrhoea Infertility Dyspareunia Breast atrophy Flushes
	Men Loss of libido, impotence Infertility Flushes Regression of secondary sexual characteristics Loss of body hair Soft testicles Fine wrinkles around the mouth
Adrenocorticotrophic hormone	Fatigue Anorexia Wt. loss Hypoglycaemia Loss of axillary and pubic hair in women
Thyroid stimulating Hormone	Wt. gain Constipation Fatigue Cold intolerance Dry skin
Vasopressin	Polydipsia Polyuria Nocturia

floor'. (b) *CT scan* – if pituitary fossa abnormal on plain radiograph or endocrinological or ophthalmological evidence of pituitary or hypothalamic lesion. A large adenoma can be detected easily in CT scans taken after IV contrast. (c) *MRI* – Advantage: Sagittal view especially useful in identifying relationship between suprasellar and infrasellar structures. Also better than CT scanning in distinguishing optic pathway from the suprasellar component of a tumor. (d) *Angiography* – may be necessary in selected cases, e.g. suspicion of the lesion being an aneurysm.

Laboratory Findings and Tests to Confirm Pituitary Insufficiency

Growth Hormone

- Low insulin-like growth factor I adjusted for sex and age
- Insulin-induced hypoglycaemia test (glucose <40 mg/dL), maximal stimulated growth hormone <3.5 µg/liter, <10 mU/liter (N >10 mU/liter)

Luteinizing Hormone and Follicle-stimulating Hormone

In women

- Reduced oestradiol with normal or reduced basal luteinizing hormone and follicle stimulating hormone

In men

- Reduced testosterone with normal or reduced basal luteinizing hormone and follicle-stimulating hormone
- Normochromic, normocytic anaemia

Thyroid Stimulating Hormone

- Reduced thyroxine or free thyroxine with normal or reduced TSH
- Elevated cholesterol

Adrenocorticotrophic Hormone

- Low or reduced basal cortisol (8–9 am) < 83 nmol/liter, (3 µg/dL), N >83 nmol/L with normal or reduced adrenocorticotropin hormone
- Hypoglycaemia (glucose <40 mg/dL)
- Eosinophilia
- Lymphocytosis
- Insulin-induced hypoglycaemia test (glucose <2.2 mmol/L, 40 mg/dL), maximal stimulated cortisol <550 nmol/L, 20 µg/dL (N >550 nmol/L, 20 µg/dL) (N > 550 nmol/L)

Vasopressin

- Reduced urine osmolality
- Raised serum osmolality and sodium
- Water deprivation test

Treatment

1. Treatment of underlying cause if possible, e.g. surgical removal of pituitary adenoma or craniopharyngioma.
2. Pituitary hormone replacement therapy

   See Table 6 for Pituitary hormone replacement therapy.
3. **Radiotherapy** – when radical removal is incomplete.

Table 6: Pituitary hormone replacement therapy

Hormone deficiency	*Replacement*	*Dose*
GH	GH	0.27–0.7 mg s.c. in evening
Gonadotropins		
Women	Estradiol Or Conjugated equine Oestrogens plus Progesterone	1–2 mg/d p.o. 0.625–1.25 µg/d p.o Estradiol 25–100 mg/d i.m.
Men	Testosterone	250 mg i.m. q 2–3 wks Transdermal 5-7.5 mg/24 hr Implant 600-800 mg q 4–6 months
TSH	Thyroxine	75–150 µg/d
Adrenocorticotropic hormone	Hydrocortisone	10 mg morning 5 mg noon 5 mg evening to 10 mg t.d.s.
Prolactin	Nil	Nil
ADH	Desmopressin	10-40 µg/d intranasal in 2–3 divided doses 300-600 µg/d p.o. in 2–3 divided doses

PITUITARY DWARFISM

Causes

Congenital (and sometimes hereditary) deficiency of the anterior pituitary growth hormone or destructive pituitary lesion in childhood. If gonadotropin output is also affected, sexual development is retarded with production of infantilism.

Clinical Features

Very slow rate of growth and hypoglycaemic attacks in childhood. No mental defect and no disproportion between relative sizes of the body and limbs of the child. Hypogonadism may be superadded. The bones are often thin and centres of ossification delayed in appearance.

Treatment

2 mg or more of human growth hormone IM two or three times weekly for an indefinite period until optimal growth or cessation of response is observed. Thyroid hormone, adrenal corticoids and testosterone or oestrogen are given only if needed.

Causes and Differential Diagnosis of Dwarfism

1. ***Familial*** – usually one of the parents has a short stature.
2. ***Constitutional*** – The parents are of normal stature and no abnormality is found on examination of the child. Diagnosis is made by elimination.
3. ***Delayed puberty*** – Delay in onset of puberty may be familial. It is commoner in boys than in girls.
4. ***Low birth weight*** – (a) Premature infants. (b) Intra-uterine growth retardation secondary either to maternal disease or poor intra-uterine environment. These children are marasmic at birth with dry skin and wrinkled facies.
5. ***Simple caloric deficiency*** – without any other nutritional deficiency.
6. ***Endocrine disorders***
   (a) *Growth hormone deficiency* – Selective deficiency of growth hormone. Body dimensions in proper proportion but stunted. Skin normal and hair distribution appropriate for sex.
   (b) *Hypothyroidism* – Plump but squat and stunted. Thick subcutaneous tissues. Coarse hair. Mental retardation. Typical facies.
7. ***Chromosomal abnormality***
   Gonadal dysgenesis (Turner's syndrome) – Hypogonadism in females at puberty with sexual underdevelopment, primary amenorrhoea, retardation of growth, webbing of skin of neck, increase in carrying angle at the elbows and osteoporosis. Buccal smear chromatin negative in 80%.
8. ***Primary skeletal disorders***
   Short-limb dwarfism:
   (a) *Achondroplasia* – Most common type. Disproportionate short stature, comparatively long trunk, and rhizomelic shortening of limbs. Large head with prominent or bulging forehead (bossing), midface hypoplasia. Trident hand. Waddling gait due to excessive lumbar lordosis and tilted pelvis.
   (b) *Diastrophic dwarfism* – Low birth weight, radiographic evidence of overlapping joints, dislocation of cervical spine and congenital heart disease.
   Short-trunk dwarfism:
   (a) *Spondyloepiphyseal dysplasia tarda* – Progressive abnormalities of spinal and epiphyseal development. Height reduction obvious by adolescence. Secondary degenerative arthritis of hip common.
   (b) *Spondyloepiphyseal dysplasia congenita* – In newborn, barrel-shaped chest, deep Harrison's groove and pigeon breast. Also flat dish-like facies, cleft palate and widely spaced eyes. In older children, the short neck makes the head appear to rest directly on the shoulders.
9. ***Chronic diseases*** – retard growth and in these cases the history and examination are usually diagnostic. (i) Vitamin D deficiency rickets. (ii) Renal acidosis – may occur in either generalised renal disease or in specific tubular defect. (iii) Coeliac disease – Stunted retarded child with anorexia, distended abdomen, wasted buttocks, anaemia and steatorrhoea. (iv) Diabetes mellitus (unregulated). (v) Glycogen storage disease. (vi) Idiopathic hypercalcaemia of infancy. (vii) Congenital heart disease. (viii) Pseudohypoparathyroidism – due to unresponsiveness of kidneys and bones to action of parathormone. Dwarfism, epilepsy, mental changes, intracranial calcification in basal ganglia, soft tissue calcification and brachydactyly.
10. ***Storage disorders***
    (a) *Hurler's syndrome* (MPS IH) – Infant large at birth, but growth rate decreases during early months of life. Coarse facies, flattening of nasal bridge, corneal clouding, hepatosplenomegaly, claw hand deformity and thoracolumbar kyphosis. Macrocephaly, macroglossia, hirsutism. Mental retardation. Severe and multiple skeletal changes on radiography.

(b) *Hunter's syndrome* (MPS II) – (i) Severe form with progressive mental retardation and death before age of 15. (ii) Milder form with survival to adulthood. Coarse facies, joint stiffness and contractures, hepatomegaly, hernia, cardiac complications, hirsutism and deafness. Radiographic features – Enlarged sella turcica, spatulate ribs, beaking of lumbar vertebrae, short and broad long bones – less pronounced than in case of Hurler's syndrome.

(c) *Morquio's syndrome* (MPS IV) – Normal at birth but growth rate restricted by 2 years of age and ceases by 12 years of age. Dwarfism, awkward gait, knock-knee, bulging sternum, flaring of rib cage, flat foot. Discoloured teeth and ligamentous laxity. Aortic regurgitation and atlantoaxial instability which may cause spinal compression and quadriplegia.

11. ***Emotional and physical deprivation*** – Growth retardation and hormone dysfunction are reversed if the child is removed to a satisfactory emotional and physical environment.
12. ***Unclassified*** – Progeria – Alopecia, bird-like features, premature senility.

ADIPOSOGENITAL DYSTROPHY (FROHLICH'S SYNDROME)

Cause – of true Frohlich's syndrome is hypothalamic lesion, commonest being craniopharyngioma.

Clinical features

1. Adiposity of buffalo type.
2. Headache, vomiting and visual disturbances if tumor.
3. Sexual infantilism pronounced in males; genital deficiency in girls not evident until puberty.
4. Hands small and fat with tapering fingers; delicate hairless skin.
5. Other symptoms of hypothalamic disturbance may be present – lethargy, polyuria, polydipsia, and sleep disorders.

X-ray skull – Deformity, erosion or compression of sella turcica and anterior clinoid process if tumour.

LAURENCE-MOON-BIEDL SYNDROME

Rare familial disorder characterized by obesity, hypogenitalism, diminished body hair, fine-textured skin, dwarfism, polydactylism, retinitis pigmentosa, and mental retardation.

THE POSTERIOR PITUITARY DISORDERS OF VASOPRESSIN SECRETION

DIABETES INSIPIDUS

Diabetes insipidus is characterized by passage of large volume (>3 liters/24 hrs) or 40 mL/kg/24 hrs, urine osmolality <300 mosmol/kg. Three primary pathogenic mechanisms are responsible for the polyuria:

1. Reduced renal response to vasopressin (nephrogenic diabetes insipidus, NDI)
2. Lack (usually partial) of osmoregulated vasopressin (cranial or hypothalamic diabetes insipidus, CDI)
3. Persistent excessive fluid intake (primary polydipsia)

Nephrogenic Diabetes Insipidus

Pathogenesis

In NDI, vasopressin fails to concentrate the urine as a result of three pathogenic mechanisms:

- V_2R defect – Vasopressin's major physiological action is on the renal distal nephron, where it binds to a seven-domain G-protein coupled membrane receptor (V_2R) to generate cyclic AMP, which activates intracellular protein kinases.
- Post-V_2R defect, intracellular or water channel proteins (aquaporin) defect
- Failure to maintain hypertonicity of the renal medullary interstitium

Causes

Causes of Nephrogenic diabetes insipidus are listed in Table 7.

Clinical Features – The X-linked disorder causes profound polyuria, dehydration, vomiting, fever, irritability and failure to thrive in infant boys.

Table 7: Causes of nephrogenic diabetes insipidus

Familial
• X-linked recessive (V_2R gene) • Autosomal dominant (aquaporin-2 gene)
Acquired
• Metabolic (hypokalaemia, hypercalcaemia) • Drugs (lithium, demeclocycline) • Osmotic diuresis (diabetes mellitus) • Post-obstructive uropathy • Solute wash-out from renal interstitium

Cranial Diabetes Insipidus

Pathogenesis – Nucleotide deletion of the vasopressin gene has been demonstrated in a number of kindreds; this causes defects in protein folding with subsequent neuronal degeneration.

Causes

See Table 8 for the causes of diabetes insipidus.

Clinical features – Patients present with sudden onset of polyuria, polydipsia and nocturia (see Table 9 for causes of pimary polydipsia). Children may develop enuresis. Hypernatraemia occurs if fluid intake is not adequate. Pregnancy can be associated with worsening polyuria or may cause transient CDI as a result of degradation of circulating vasopressin by placental enzyme vasopressinase. In traumatic DI, triphasic response may occur. Initial polyuria, prolonged antidiuresis and final polyuria.

Clinical features – Excessive drinking leads to polydipsia, polyuria, and occasionally nocturia. Patients may drink huge volumes of fluid (> 20 liters/day) which causes transient hyponatraemia because the kidney diluting capacity is exceeded by the large fluid load.

Diagnosis of Diabetes Insipidus

1. ***Urine volume*** – It is necessary to confirm excessive urine output (> 3 liters/24 hrs).
2. ***Blood glucose, serum calcium and potassium*** estimation to exclude other causes of polyuria.
3. ***Serum uric acid*** is elevated in hypothalamic diabetes insipidus.
4. ***Fluid deprivation/desmopressin test*** (Table 10)

   Patient preparation
   - Normal fluid overnight
   - Avoid caffeine and smoking
   - Weigh patient

   Fluid deprivation (dehydration) phase
   - Obtain blood and urine for osmolality measurements and urine volume at 8 am
   - Restrict fluid for upto 8 hours
   - Weigh patient every 2 hrs
   - Obtain blood and urine for osmolality and urine volume
   - Stop test if wt. loss > 5% of starting wt. or intolerable thirst
   - Beware of surreptitious drinking

   Desmopressin phase
   - Inject desmopressin 2 µg IM.
   - Patient is allowed to eat and drink upto 2 × volume passed during deprivation phase.
   - Obtain blood and urine for osmolality and urine volume at 8 pm and 8 am the next day.
5. ***Hypertonic saline infusion test*** – Plasma measurements of vasopressin and osmolality during 2-hr infusion of 5% (855 mmol/liter) saline at a rate of 0.04–0.06 mL/kg/minute to confirm diagnosis of CDI.

Table 8: Causes of diabetes insipidus

Familial
• Autosomal dominant
• DIDMOAD syndrome (CDI, DM, optic atrophy, deafness)
Cerebral malformation
• Septo-optic dysplasia
• Laurence-Moon-Biedl syndrome
Acquired
• Trauma (head injury, surgery)
• Tumor (craniopharyngioma, pinealoma, hypothalamic metastasis, pituitary)
• Lymphocytic infiltration of stalk
• Autoantibodies to vasopressin magnocellular neurons
• Granulomas (tuberculosis, sarcoidosis, histiocytosis)
• Vascular (aneurysms, sickle-cell disease, Sheehan's syndrome)
• Infection (meningitis, encephalitis)
• Idiopathic

Table 9: Causes of primary polydipsia

• Compulsive, habitual drinking
• Psychosis
• Drugs (lithium, carbamazepine)
• Head injury
• Granuloma (sarcoidosis)
• Idiopathic

Table 10: Interpretation of fluid deprivation/desmopressin test

After fluid deprivation	*After desmopressin*	*Diagnosis*
<300	>750	CDI
<300	<300	NDI
>750	>750	PP
300–750	<750	? Partial CDI
		? Partial NDI
		? Primary PD

Urine osmolality mOsmol/kg

6. ***Therapeutic trial of low-dose desmopressin*** – 10–20 µg intranasally for 2 weeks is an alternative method of confirming the diagnosis. In case of CDI there is symptomatic improvement, NDI no effect, progressive hyponatraemia in case of primary polydipsia.
7. ***Additional investigations*** – Once diagnosis of diabetes insipidus is confirmed, the underlying cause must be sought. CDI patients must have pituitary and hypothalamic imaging (preferably MRI) to look for a structural lesion. In CDI, the normal hyperintense signal of the posterior pituitary is lost on T_1-weighted MRI.

Management

NDI – Polyuria from metabolic and blood electrolyte disturbances causing NDI is often reversible once these are corrected. In familial NDI, hydration should be maintained by adequate fluid intake. Urine output can be reduced by upto 50% with a combination of indomethacin and thiazide diuretic. High dose desmopressin may be efficacious in partial NDI.

CDI– Desmopressin is the drug of choice. Daily dose – Oral 50–1200 µg in divided doses, intranasal 5–40 µg by spray in one to three doses, parenteral 1–2 µg i.m. Desmopressin in excess over prolonged period causes hyponatraemia.

Primary polydipsia – Water restriction, with treatment of any associated psychiatric disorder.

Differential Diagnosis

(of Polyuria and Polydipsia)

1. *Diabetes mellitus* – Urine volume rarely exceeds 3 liters per day. Presence of sugar in urine and elevated blood sugar.
2. *Chronic kidney failure* – Urine not in such large quantities, often nocturia. Blood pressure high. Other urinary findings like albuminuria and casts. Polyuria resistant to pitressin. Specific gravity fixed at about 1,010 in chronic kidney failure.
3. *Hypercalcaemia* – High serum calcium. Inability to concentrate urine.
4. *Hypokalemia* – Polyuria may be seen in the presence of decreased values for serum potassium. Symptoms of drowsiness, anorexia, nausea and marked muscular weakness. Electrocardiogram – prolongation of QT interval, T wave inversion and sagging of ST segment. Correction of electrolyte disturbance results in return to normal.
5. *Caffeine idiosyncrasy* – This runs in families. Polyuria ceases if only water is drunk.
6. *Drugs* – (besides diuretics) – antihistamines, carbamazepine, vitamin D excess, demethyl-chlortetracycline.

(Also refer to Polyuria in Chapter 8).

ESSENTIAL HYPERNATRAEMIA

Causes: Various types of organic disease affecting pituitary hypothalamic region.

Clinical features – Sustained hypernatraemia, decreased thirst. Some patients show anterior pituitary dysfunction, obesity, hyperlipidaemia and episodic muscle weakness.

Investigations – Normal kidney function, no signs of hypovolaemia and patient can form concentrated urine with dehydration. Vasopressin levels are inappropriately low for the serum osmolality.

SYNDROME OF INAPPROPRIATE ANTIDIURESIS (SIAD)

The syndrome of SIAD is one common cause of dilutional hyponatraemia. The main features are hyponatraemia with corresponding low plasma osmolality, urine osmolality greater than plasma osmolality, persistent urinary excretion of sodium, absence of hypotension and hypovolaemia and of oedema-forming states and normal kidney and adrenal function.

Pathogenesis – Administration of vasopressin and water causes a dilutional hyponatraemia in which the patient remains normovolaemic but becomes hypotonic and usually has persistent excretion of sodium. Urine osmolality is greater than plasma osmolality. The syndrome of inappropriate antidiuresis is the term used for these patients who must also retain normal kidney and adrenal function and must not be hypotensive or hypovolaemic. See Table 11 for the causes of SIADH.

Table 11: Causes of SIADH

Tumors – Carcinoma of bronchus, also of duodenum, pancreas or prostate. Lymphoma, leukemia, thymoma.
Chest disorders – Pneumonia, tuberculosis, emphysema, cystic fibrosis, asthma, pneumothorax, lung abscess, positive pressure ventilation.
CNS disorders – Head injury, meningitis, encephalitis, Guillain-Barre syndrome, brain tumor, brain abscess, cerebral hemorrhage, cavernous sinus thrombosis, hydrocephalus, cerebral or cerebellar atrophy, Shy-Drager syndrome.
Drugs – Thiazide diuretics, vincristine, vinblastine, cyclophosphamide, chlorpropamide, carbamazepine, phenothiazines, tricyclic antidepressants, oxytocin, vasopressin.
Miscellaneous – Idiopathic, acute porphyria, hypothyroidism, glucocorticoid deficiency, acute psychosis.

Diagnostic criteria

1. Dilutional hyponatraemia (plasma osmolality appropriately low compared to plasma sodium).
2. Urine osmolality > plasma osmolality.
3. Persistent renal sodium excretion.
4. Absence of hypotension, hypovolaemia and oedema forming states.
5. Normal renal and adrenal function.

Treatment – (a) Of cause if possible. (b) Restriction of fluid intake to 0.5–1 liter/day. (c) If water restriction poorly tolerated Demeclocycline 1–2 g/day in divided doses but its maximal effect may be delayed for 3–6 weeks. It induces nephrogenic diabetes insipidus. (d) Induction of natriuresis and diuresis with frusemide and sodium chloride supplements. (e) Inhibition of neurohypophyseal vasopressin secretion with phenytoin. (f) Slow infusion of hypertonic saline. Plasma sodium should not be raised faster than 100 mmol/liter/24 hours. (g) The other treatment is to reduce body water by giving an AVP receptor-2 antagonist (vaptan) to block the antidiuretic effect of AVP and increase urine output. One of the vaptans, a combined V2/V1A antagonist (Conivaptan), has been approved for short-term, in-hospital IV treatment of SIADH.

2. OBESITY

Obesity describes a weight of 120% or above. Obesity is often expressed in terms of body mass index (BMI), but pathophysiologically may be considered to be present when sufficient body fat has accumulated to adversely affect health.

BMI is calculated by measuring an individual's weight in kg., and dividing his/her height in meters square (kg/m_2). Table 12 gives WHO classification of obesity.

CAUSES OF OBESITY

Inherited Causes (Table 13)

Environmental causes

High-energy diets – Increased consumption of energy dense foods. Less regular eating patterns, shorter meals and increased snacking may also contribute.

Physical Inactivity

Other causes

Endocrine disease

(a) *Pituitary* - (i) Frohlich's syndrome. (ii) Puberty adiposity. (iii) Climacteric both males and females. (iv) Pregnancy.

Table 12: WHO classification of overweight

Classification	*BMI (kg/m²)*	*Associated health risk*
Underweight	<18.5	Low (but risk of other clinical problems increased)
Normal	18.5–24.9	Average
Overweight		
Pre-obese	25–29.9	Increased
• Obese class I	30–34.9	Moderately increased
• Obese class II	35–39.9	Severely increased
• Obese class III	≥40	Very severely increased

Table 13: Inherited causes of obesity

Condition	*Key features*	*Genetic defect*
Prader-Willi syndrome	Short stature, small hands and feet, almond-shaped eyes, learning difficulties, hypogonadism	Paternally imprinted gene, chromosome 15
Bardet-Beidl syndrome	Mental retardation, renal dysplasia, polydactyly, hypogonadism	Several described (chromosomes 4, 11, 15, 16)
Leptin deficiency	Severe hyperphagia, hypogonadism	Leptin gene
Leptin receptor mutations	Severe hyperphagia, hypogonadism	Leptin receptor gene
Preopiomelanocortin defects	Moderate obesity, red hair	Proopiomelanocortin gene
Melanocortin-4 receptor defects	Severe early-onset obesity	Melanocortin-4 receptor gene
Prohormone convertase 1 deficiency	Failure to process insulin and Proopiomelanocortin	Pro-hormone convertase 1 gene

(b) *Thyroid* – Hypothyroidism.

(c) *Adrenal cortex* – Cushing's syndrome.

(d) *Gonads* – Eunuchoidism sometimes. Polycystic ovary syndrome.

(e) *Pancreas* – Islet-cell tumors and chronic hypoglycaemia often associated with adiposity.

(f) *Hypothalamus* – Encephalitis, meningo-encephalitis, craniopharyngioma (including Frohlich's syndrome). Third ventricle tumors and cerebral injuries may also produce adiposity by involvement of hypothalamus.

Drugs (Table 14).

TYPES OF BODY FAT DISTRIBUTION

Pear type – Fat accumulates mainly around hips and thighs (gynoid distribution) characteristic of females.

Apple type – Fat storage mainly in the abdomen (android distribution), found in both sexes.

MORBID EFFECTS OF OBESITY

See Table 15 for the effects of obesity.

MANAGEMENT OF OBESITY AND OVERWEIGHT

1. **Exercise** – is useful as a supplement to dieting unless there is a medical contraindication.
2. **Diet** – Rigid dieting is best treatment. 800 to 900 calories per day. It must contain amounts of all essential foodstuffs. Bulkiness of food is important as the patient needs to be satiated. People tend to ingest a constant volume of food regardless of caloric or macronutrient content. Adding water or fiber to a food decreases its energy density by increasing weight without affecting caloric content. Examples of foods with low-energy density include soups, fruits, vegetables. *Foods to be avoided* – bread and anything made with flour, cereals, potatoes and other whole root vegetables, foods containing much sugar, all sweets and salt. Fatty foods

Table 14: Drugs causing obesity

• Anticonvulsants:	Sodium valproate, phenytoin, gabapentin
• Antipsychotics:	Chlorpromazine, risperidone, olanzapine
• Antidepressants:	Citalopram, mirtazapine
• β-blockers	Atenolol
• Corticosteroids	Prednisolone, dexamethasone
• Insulin	All formulations
• Serotonin antagonists	Pizotifen
• Sex steroids	Medroxyprogesterone acetate, progesterone, combined oral contraceptives
• Oral	Glibenclamide, hypoglycaemic gliclazide, repaglinide, pioglitazone
• Protease	Indinavir, ritonavirinhibitors

Table 15: Effects of obesity

1. *Endocrine and metabolic diseases*
   - Metabolic and insulin resistance syndrome – Features include insulin resistance with associated hyperinsulinaemia, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidaemia characterised by hypertriglyceridaemia and low serum HDL cholesterol levels.
2. *Cardiovascular disease*
   - Hypertension
   - Coronary heart disease
   - Cerebrovascular and thromboembolic disease
3. *Pulmonary disease (Table 16)*
   - Restrictive lung disease
   - Obstructive sleep apnoea
4. *Musculoskeletal disease*
   - Gout
   - Osteoarthritis
5. *Neurologic disease*
   - Idiopathic intracranial hypertension (pseudotumour cerebri)
6. *Cataracts*
7. *Gastrointestinal, biliary and pancreatic disease*
   - Gastrooesophageal reflux disease
   - Gallstones
   - Pancreatitis
8. *Liver disease*
   - Nonalcoholic steatohepatitis
9. *Genitourinary disease in women*
   - Irregular menses
   - Amenorrhoea
   - Infertility
10. *Pregnancy* – Neural tube defects, perinatal mortality, pre-eclampsia, gestational diabetes, pre-term labour, caesarean sections, deep vein thrombosis.
11. *Malignancy* – Sex-hormone-sensitive cancers such as cancer of colon, rectum and prostate in men and the breast, ovary, endometrium and cervix in women.
12. *Skin* – Dermal and sweat rashes.
13. *Psychosocial* – Psychological and emotional stress appears to be more common.
14. *Postoperative complications.*

Table 16: Classification of obesity-related respiratory compromise

Stage 1 - BMI <27 kg/m²
• Normal forced vital capacity • Reduced end-expiratory reserve volume • Low-normal $PaCO_2$ • Recumbency in sleep may impair ventilation and vascular perfusion • Impaired exercise capacity
Stage 2 - BMI 27-35 kg/m²
• Restrictive defect, forced vital capacity 80% predicted • Reduced lung and chest wall compliance • End-expiratory reserve volume almost equals closing volume • Ventilation/perfusion mismatch • Increased alveolar-arterial gradient • Impaired gas exchange during sleep • Mild daytime hypercapnia indicative of sleep-disordered breathing • Dyspnoea on exercise and at rest
Stage 3 - BMI >35 kg/m²
• Pulmonary hypertension and right heart failure • Hypercapnoea • Obesity-hypoventilation syndrome • Obstructive sleep apnoea

like cream, butter, fat. Beans and pork. Fluids not more than 2 pints a day. No restriction of – meat, fish and fowl, all green vegetables, eggs and fruits.

3. **Drugs:** (a) *Sibutramine* – inhibits reuptake of noradrenaline and serotonin, promoting and prolonging satiety. Dose – 10 mg starting, may be increased to 15 mg daily if inadequate wt. loss on 10 mg, or decreased to 5 mg if patient dose not tolerate 10 mg dose. Side-effects – Dry mouth, constipation, insomnia, noradrenergic effects of the drug can cause tachycardia and increased blood pressure. Sibutramine should be avoided in patients with arrhythmia or uncontrolled hypertension. (b) *Orlistat* – is an intestinal lipase inhibitor. It generates malabsorption of 30% dietary fat. Dose – 120 mg with each of the main meals, to be taken immediately after a meal or one hour later. Side effects – are related to effect of fat malabsorption such as loose stools, faecal urgency and flatus. The drug should be used only in patients who can adhere to a low-fat diet. (c) *Rimonabant* – is cannaboid receptor antagonist. Blockade with the drug produces wt. loss and wt.—independent improvement of some cardiovascular risk factors. Dose – 20mg daily. Side effects are minimal. (d) *Lorcaserin* - is a selective 5-HT2C receptor agonist, by activating the 5-HT2C receptor, lorcaserin is thought to decrease food intake through the pro-opiomelanocortin system of neurons. Dose – 10 mg bd. (e) *PHEN/TPM* - is a combination drug that contains a catecholamine releaser (phentermine) and an anticonvulsant (topiramate). Topiramate was found to have weight loss as an unintended effect when used as an anticonvulsant.
4. **Bulk agents** – which provide essential nutrients and produce a feeling of satiation.
5. **Psychotherapy** – Motivation for weight reduction must be cultivated in the patient's mind. Neurotic subjects are known to seek relief from their anxiety by eating.
6. **Liposuction –** Large volume liposuction is possible, however upper limit that can be removed remains to be defined. The removed fat should not be considered as lost weight.
7. **Surgery** –
   - *Laparoscopic adjustable gastric banding* – (a) A laparoscopic implantation of a silastic band around the stomach just below the gastrooesophageal junction. (b) This creates an hour-glass effect. Since the outlet is small, food stays in the pouch longer and patient feels satisfied for a longer time. (c) The band can be adjusted by injecting fluid into as an outpatient. (d) It is 100% reversible.
   - *Laparoscopic sleeve gastrectomy* – (a) This is an operation in which approximately 2/3rd of the left side of the stomach is removed. (b) The stomach thus takes the shape of a tube or sleeve. (c) It removes that part of the stomach that contains Ghrelin hormone, hence decreases the appetite. (d) It is irreversible.
   - *Laparoscopic Roux-en-y bypass* (a) A small stomach pouch is created by stapling the stomach. This causes restriction of food intake. (b) Next a "Y-shaped" section of the small intestine is attached to the pouch to allow food to bypass the first part of small intestine by malabsorption. It is reversible.

Advantages

- In restrictive procedures patients have early satiety with small meals thereby restricting total calorie intake.
- (a) In malabsorptive procedures along with small meals the bypassed portion reduces absorption as well. It also causes good hormonal changes leading to resolving morbidities like diabetes, hypertension, sleep apnoea, etc. (b) The band or staples do not cause cancer. (c) Bariatric surgery improves fertility.

Complications

- Bleeding
- Infection
- Leakage

3. THYROID DISEASE

THYROTOXICOSIS

The term *thyrotoxicosis* refers to the clinical syndrome of hypermetabolism and hypersensitivity which result from excessive amount of thyroid hormones. The term *hyperthyroidism* is used to denote sustained increase in thyroid hormone biosynthesis and secretion by the thyroid gland. Thyrotoxicosis can occur without hyperthyroidism when it is caused by thyroiditis or exogenous thyroid hormone administration. See Table 17 for the causes of thyrotoxicosis. Table 18 describes complications of hyperthyroidism in pregnancy.

GRAVES' DISEASE

Graves' disease is an autoimmune disorder in which thyroid stimulating immunoglobulin (TSI) binds to and stimulates thyroid stimulating hormone (TSH) receptor on thyroid cell membrane resulting in excessive synthesis and secretion of thyroid hormone. Table 19 lists potential risk factors for Graves' disease and Table 20 describes its clinical features.

Table 17: Causes of thyrotoxicosis

Primary hyperthyroidism
- Graves' disease
- Toxic multi-nodular goiter
- Toxic adenoma
- Functioning thyroid carcinoma metastasis
- Activating mutation of TSH receptor
- Struma ovarii
- TSH secreting pituitary adenoma
- Iodine excess (Jod-Basedow phenomenon)
- Activating mutation of Gsa (McCune-Albright syn.)

Thyrotoxicosis without hyperthyroidism
- Subacute thyroiditis
- Silent thyroiditis
- Other causes of thyroid destruction: Amiodarone, radiation, infarction of adenoma
- Ingestion of excess thyroid hormone (thyrotoxicosis factitia)

Secondary hyperthyroidism
- TSH secreting pituitary adenoma
- Thyroid hormone resistance syndrome
- Chronic gonadotropin-secreting tumor
- Gestational thyrotoxicosis
- Thyrotoxicosis factitia

Table 18: Complications of hyperthyroidism in pregnancy

- Increased and recurrent pregnancy loss
- Preterm delivery
- Pre-eclampsia
- Foetal growth restriction
- Foetal thyroid hyperfunction or hypofunction
- Foetal goiter from excessive antithyroid drug therapy
- Neonatal thyrotoxicosis
- Increased perinatal and maternal mortality
- Decreased IQ of offspring due to excessive use of antithyroid drugs

Table 19: Potential risk factors for Graves' disease

1. Genetic susceptibility – Role of hereditary factors is evidenced by increased incidence of other autoimmune disorders in members of patients' families.
2. *Emotional stress.*
3. *Gender* – Females more prone than men (7 to 10:1) ratio.
4. *Pregnancy* – Iodine containing drugs.
5. *Iodine and drugs* – Amiodarone and iodine containing contrast media may precipitate Graves' disease.
6. *Irradiation,* e.g. radioactive iodine for multinodular goiter.

Table 20: Clinical features

Thyrotoxicosis (found in thyrotoxicosis of any cause)

Symptoms
- Weight loss with increased appetite
- Heat intolerance and sweating
- Fatigue and weakness
- Hyperactivity, irritability, dysphoria, insomnia
- Dyspnoea
- Oligomenorrhoea, loss of libido
- Diarrhoea/hyperdefecation
- Polyuria

Signs
- Tremor, hyper-reflexia
- Tachycardia, atrial fibrillation in elderly
- Warm moist skin
- Lid retraction, lid lag (causing a stare)

Contd...

Contd...

• Muscle weakness, proximal myopathy • Gynaecomastia
Specific for Graves' disease
• Family or personal history of immune disorders (e.g. vitiligo, pernicious anaemia, type 1 diabetes mellitus, coeliac disease, myasthenia gravis)
• Ophthalmopathy
Grittiness, increased tear production
Periorbital oedema
Chemosis (conjunctival oedema)
Proptosis (unilateral in 5–10%)
Diplopia caused by extraocular muscle dysfunction
Impaired visual acuity/visual fields (caused by optic nerve compression)
Corneal ulceration
• Pretibial myxoedema
• Thyroid acropachy (resembling finger clubbing)
Strongly associated with ophthalmopathy suggesting a shared pathogenesis that is most likely the result of fibroblast activation by cytokines from autoreactive T cells.
Thyroid acropachy in Graves' disease. The hypermetabolic state leads to axial bone destruction presumably secondary to enhanced neoclast activity. Acropachy is not to be confused with clubbing which is usually painless.

Laboratory Evaluation of Thyroid Function

Tests for Testing Thyroid Function

- Serum based methods for measuring both total (T4 and T3) and free (T4 and T3) thyroid hormone concentrations (Table 21)
- Measurement of thyroid hormone binding proteins – Thyroid Binding Globulin (TBG), Transthyretin (TTR)/ Prealbumin (TBPA) and Albumin as well as for the pituitary thyroid stimulation. Thyroid stimulating hormone (TSH) and the thyroid hormone precursor protein Thyroglobulin (Tg)
- Tests to determine thyroid antibodies – Thyroid peroxidase antibodies (TPOAb), Thyroglobulin antibodies (TgAb) and TSH receptor antibodies.

Testing for Thyroid Dysfunction

TSH is the first test to be performed since it is the single best test for thyroid function. The most advanced (third generation) chemiluminescent TSH assays can measure values <0.1 mU/L, thus aiding detection of subclinical thyrotoxicosis. A normal TSH value is sufficient indicator to stop further thyroid function in most cases. However, in cases suggestive of possible hypothalamic pituitary disease (central), a free T4 level estimation is desirable. See Table 22 for the causes of abnormal serum TSH concentrations.

Table 21: Values of thyroid function test

Test	*Range*
TSH	0.5–4.7 mμ/L
T3	0.92–2.78 nmol/L
FT3	0.22–6.78 nmol/L
T4	58–140 nmol/L
FT4	10.3–35 pmol/L

Table 22: Causes of abnormal serum TSH concentrations

TSH below normal	*TSH above normal*
Primary hyperthyroidism	Primary hypothyroidism
Pituitary/hypothalamic disease with central hypothyroidism thyroid (TSH unreliable)	Pituitary thyrotroph adenoma, pituitary resistance to hormone
Prolonged thyrotroph cell suppression after recent hyperthyroidism in euthyroid or hypothyroid patient	Generalized thyroid hormone resistance
Old age	Thyrotoxicosis from rapid correction of severe hypothyroidism with parenteral T4
Problems with T4 treatment: Overdosage for fatigue or overweight diseases. Altered T4 clearance because of drugs or disease	Old age
Severe systemic illness (Sick euthyroid state)	Drugs, e.g. amiodarone
	Problems with T4 treatment: under dosage, altered GI absorption or altered clearance of T4 because of drugs
	Recovery phase after severe systemic illness

Indications for TSH Testing

- Patients presenting with suspected goiters
- As screening test for congenital hypothyroidism
- Patients with AF, dyslipidaemia, osteoporosis and infertility
- As screening test for thyroid disorders in patients with unclear diagnosis

Diagnosis

1. ***Serum T3, T4*** – (Refer)
2. ***Thyroid antibodies*** – (Refer)
3. ***Serum thyroperoxidase (TPO)*** – Increased concentrations of TPO antibodies indicate autoimmune thyroid disorder and a raised TSI Graves' disease.
4. ***Other laboratory abnormalities*** – Hyperglycaemia, hypercalcaemia, elevated alkaline phosphatase, leucocytosis and elevated liver enzymes may occur.
5. ***Imaging***
   - Nuclear medicine scanning – Radioactive uptake and scanning. After ingestion of I^{131}, the emitted radiation allows external detection, calculation of fractional uptake and scintigraphy imaging of thyroid gland.
   - Thyroid ultrasound – Can identify thyroid nodule and goiter. Also, Doppler index of blood flow percentage is used to distinguish between Graves' disease and thyrotoxicosis caused by non-hypermetabolic destructive thyrotoxicosis.

Differential Diagnosis:

Toxic nodular goiter (Table 23)

Total T4. In some clinical conditions, Total T3 and T4 may be elevated (Table 24) while in the thyroid functional state free T3 and T4 levels may be normal –

1. Hereditary abnormalities of binding proteins, e.g. TBG deficiency or TBG excess, abnormal albumin and transthyretin levels.
2. Acquired deficiency of binding proteins, e.g. nephrotic syndrome causing protein loss, impaired production of proteins in severe liver disease and therapy with androgens or anabolic steroids.
3. Drug-induced alterations in T4 binding to TBC, e.g. salicylates, phenytoin.
4. Presence of T4 antibodies.

Radioimmunoassay measurements overcome many of these problems.

Table 23: Differences between Graves' disease and toxic nodular goiter

	Graves' disease	*Toxic nodular goiter*
Age	Younger	Older
Gland	Smooth, diffuse enlargement	Nodular, irregular
Eye signs	Common	Rare
Cardiac involvement	Uncommon	Common
Pressure symptoms	Uncommon	Common
Autoimmune disease	Common	Uncommon

Total T3. Indications for free T3 / total measurements –

1. In patients suspected of having thyrotoxicosis.
2. In patients taking drugs that inhibit peripheral conversion of T4 to T3, e.g. dexamethasone, propranolol, propylthiouracil, amiodarone.

Testing Both TS4 and FT4

Clinical situations

- Optimising the therapy in newly diagnosed patient with hypothyroidism
- Diagnosing and monitoring thyroid disorders in pregnancy
- Monitoring patients with hypothyroidism in early months after treatment
- Diagnosing and monitoring treatment for central hypothyroidism
- Endo-organ thyroid hormone resistance
- Sick euthyroid state
- Women with type 1 diabetes should have their thyroid function including serum TSH, FT4 and thyroid peroxidase antibody test status established preconception at booking when pregnant and at 3 months post-partum.

Thyroid Autoimmunity. Thyroid Specific Autoantibodies

1. *Thyroid peroxidase autoantibodies* (TPOAb). Clinical use – Approximately 70–80% of patients with Graves' disease and virtually all patients with Hashimoto's, atrophic thyroiditis or post-partum thyroiditis have TPOAb detected. A euthyroid patient with detectable TPOAb is at a risk of development of hypothyroidism.
2. *Thyroglobulin autoantibodies* (TgAb) – is primarily an adjunct test for serum Tg estimation.
3. *TSH receptor autoantibodies* (TRAb). Clinical uses – In the differential diagnosis of hyperthyroidism, prediction of foetal and neonatal thyroid dysfunction due to transplacental passage of normal TRAb and prediction

Table 24: Causes of elevated serum thyroxine concentration

• Thyrotoxicosis Increased serum protein binding Increased serum thyroxine binding globulin concentrations
• Inherited Estrogen: Pregnancy, exogenous humoral production Hepatitis, hepatoma HIV infection Psychiatric and medical illness
• Drugs: Heroin, methadone, 5-Flurouracil, amiodarone, propranolol

of course of Graves' disease treated with antithyroid drugs.

Thyroid Function Tests in Special Situations

1. Patients presenting with AF, hyperlipidaemia, osteoporosis, subfertility.
2. Type 1 diabetes in women raises the likelihood of developing postpartum thyroid dysfunction by three times.
3. Women with past history of postpartum thyroiditis.
4. Patients with diabetes, Type 1 DM - yearly thyroid function tests. Type 2 DM - at diagnosis.
5. Down syndrome and Turner's syndrome. Yearly tests because of high incidence of hypothyroidism.
6. Patients receiving Amiodarone and Lithium. Assessment at beginning of therapy and thereafter every 6–12 months during treatment and till 12 months after cessation of therapy with amiodarone and every 6–12 months during therapy with lithium.
7. Post neck irradiation or surgery – Assessment annually.
8. Destructive treatment of thyrotoxicosis by radioiodine or surgery. Assessment 4–6 weeks after treatment, followed by quarterly and annually thereafter.
9. Treatment with antithyroid drugs. Thyroid function every 1–3 months to determine if stable hormonal concentrations have been reached when antithyroid therapy is started and thereafter if long term treatment is required.
10. Patients on thyroxine therapy, regardless of the cause, TSH annually. In pregnant women, dose may need to be increased by 50 µg/d to maintain TSH level.

Management: of Thyrotoxicosis

1. 'Antithyroid' drugs

Thionamides

Mode of action – Carbimazole and Propylthiouracil inhibit iodine organification by thyroid peroxidase, reducing T_3 and T_4 production. Propylthiouracil also inhibits conversion of T_4 to T3 in severe thyrotoxicosis. These drugs also reduce TSH receptor-stimulating antibody levels, which probably accounts for sustained remission in 40–50% of patients with Graves' disease.

Indications – (1) All subjects preoperatively. (2) Children and adolescents with first attack of thyrotoxicosis. (3) Thyrocardiacs and thyrocachectics. (4) Patients with small toxic multinodular goiters. (5) Pregnancy with hyperthyroidism. (6) Patients who for some reason cannot have surgery, and radioactive iodine is not available or justified because of young age of the patient. (7) Mild cases.

Contraindications – (1) Hypersensitivity. (2) Anaemia or leucopenia. (3) Kidney or liver disease.

Dosage

(a) Titration regimen – Initial dose: High doses (carbimazole 40–60 mg/day, or propylthiouracil 300–450 mg/day), then gradually reduced every 4–8 weeks based on FT4 levels. When FT4 levels are normal carbimazole 5–15 mg/day or propylthiouracil 50 mg/day. Treatment is usually continued for 18–24 months, with regular checking of FT4 and TSH levels.

(b) Block- replace regimen – Carbimazole 40 mg/day or propylthiouracil 300 mg/day is maintained throughout and hypothyroidism avoided by addition of T4 100 µg/day. Three to four weeks after starting treatment, T4 dose is subsequently adjusted based on FT4 levels. This regimen can be given for 6 months with a remission rate similar to that of the titration regimen. Patients are reviewed regularly in the year after stopping antithyroid drugs, because 70% of relapses occur during this period.

Duration of therapy – Tr. is continued for 18–24 months, with regular checking of T_4 and TSH levels every 3 months.

Side–effects – Abnormal sense of taste, pruritus, arthralgias and urticaria, hepatitis. The most serious is agranulocytosis related to dose of methimazole (> 30 mg/day).

Other antithyroid drugs – (a) β-*blockers* (propranolol 60–120 mg/day) relieve symptoms such as tachycardia, tremor and anxiety. β-blockade should be used as primary treatment only in patients with thyrotoxicosis due to thyroiditis. (b) *Dexamethasone* 8mg/day may be used to inhibit conversion of T_4 to T_3 in patients with thyroid storm (the most severe form of thyrotoxicosis). Also to relieve severe anterior neck pain and to restore euthyroidism in patients with painful subacute thyroiditis. (c) *Inorganic iodine* (SSKI or Lugol's solution) decreases synthesis of thyroid hormone and release of hormone from the thyroid in the short term. It is used to reduce thyroid vascularity before thyroidectomy, and in thyroid storm. (d) *Lithium* carbonate inhibits thyroid hormone secretion. Dose: 300–450 mg tds to provide temporary control of thyrotoxicosis in patients who are allergic to thionamides and iodide. Another short term use for lithium has been as an adjunct to radioiodine therapy in that the drug slows release of iodine from the thyroid. (e) *Potassium perchlo-*

rate 500 mg bd inhibits iodine uptake by the thyroid gland by direct inhibition of the sodium iodine supporter. It can be combined with thionamides. Side effects – Aplastic anaemia, nephrotic syndrome with prolonged treatment. Advantages – Particularly useful in patients with iodine-induced thyrotoxicosis as seen in patients with amiodarone induced thyrotoxicosis. (f) *Cholestyramine* decreases reabsorption of thyroid hormones from the enterohepatic circulation. Dose – 4 gm qds in combination with methimazole or PTU.

2. Radioactive iodine

Mode of action – Destruction of functional thyroid cells or inhibition of their ability to replicate.

Indications – (i) In patients over the age of 40 it is the treatment of choice. (ii) Toxicity recurring after previous subtotal thyroidectomy. (iii) Very nervous patients who fear surgery. (iv) Patients with severe thyrotoxic heart disease or other debilitating conditions. (v) Young patients who have relapsed following antithyroid drugs or who have shown sensitivity reactions to them.

Contraindications – (i) Patients under 45 years of age because of high incidence of hypothyroidism (except recurrence of thyrotoxicosis after subtotal thyroidectomy or severe cardiac or other associated disease). (ii) During pregnancy and lactation.

Advantages – (i) Simple procedure. (ii) Patient may be ambulant. (iii) Usually no radiation sickness or initial swelling of the thyroid gland. (iv) No skin changes. (v) Successful in almost all cases. (vi) Cheap. (vii) Useful in uncooperative patients and those with extremely large goiters. (viii) Also useful when serious toxic reactions have followed therapy with other compounds. (ix) No mortality.

Disadvantages – (i) High incidence of permanent hypothyroidism. (ii) Optimum benefit does not take place until about 3 months.

Dose – Antithyroid drugs are given and/or shortly after ^{131}I to prevent thyroid storm. Antithyroid drugs must be stopped for a minimum of 3–5 days before ^{131}I to allow uptake of the isotope 555 MBq to ablate the thyroid. High doses are used for large goiters in severely thyrotoxic patients.

Side effects – Mild neck pain, anterior neck pain caused by radiation thyroiditis or worsened thyrotoxicosis, owing to leakage of preformed thyroid hormones from the damaged thyroid gland. Graves' ophthalmopathy may develop or worsen after treatment especially in smokers and in patients with severe hyperthyroidism. Graves' ophthalmopathy can be prevented by simultaneous administration of glucocorticoids.

3. Surgery (Subtotal thyroidectomy)

See Table 25 for the indications of surgery.

Table 25: Indications of surgery

Absolute
Suspicion of biopsy proven malignant nodules
Co-morbidity requiring surgery, e.g. hyperparathyroidism
Pregnancy or lactation
Young children
Severe intolerance to antithyroid medications
Large compressive/obstructive goiter
Relative
Severe Graves' ophthalmopathy
Patients desiring pregnancy within 6–12 months of treatment
Patients unable to continue close follow-up
Patients incompletely treated by radioactive iodine ablation

GRAVES' DISEASE

See Table 26 for the symptoms and signs of thyroid ophthalmopathy.

Table 26: Thyroid ophthalmopathy

Symptoms	
Dry eyes	Field loss
Puffy eyelids	Dyschromatopsia
Proptosis	Photopsia on up gaze
Eyelid retraction	Ocular pressure or pain
Diplopia especially at extreme gaze	Lacrimation
Visual loss	
Signs	
Lid signs: Lid lag and lid retraction resulting in a staring look.	
Soft tissue signs – Eyelid oedema, conjunctival erythema and chemosis.	
Proptosis – Combined with lid retraction and inferior rectus restriction leads to corneal exposure and ulceration.	
Restrictive extraocular myopathy. Recti involved in decreasing order of severity and frequency are inferior rectus, superior rectus and lateral rectus.	
Strabismus often represents as hypotropia or esotropia. In patients with thyroid ophthalmopathy and exotropia, possibility of concurrent myasthenia gravis should be considered.	
Optic nerve compression – Compressive thyroid optic neuropathy.	

Contd...

Contd...

Glaucoma may result from decreased episcleral venous flow.
Other eponymous signs • Vigouroux sign (Eyelid fullness) • Stellwag's sign (Incomplete and infrequent blinking) • Graves' sign (Resistance to pulling down the retracted upper lid) • Joffroy sign (Absent creases on the forehead on superior gaze) • Mobius sign (Poor convergence) • Ballet sign (Restriction of one or more extraocular muscles)
Deep glabellar rhytides – Due to hypertrophy of brow depressor muscles compensating for lid retraction

Management

Discomfort

- Artificial tears during the day
- Simple eye ointment at night
- Dark glasses with side frames

Medical therapy: (1) No smoking. (2) Reduction of morning lid oedema by sleeping on a bed with its head slightly raised. (3) Radiotherapy. (4) Glucocorticoids. (5) Antioxidants. (6) Somatostatin analogues. (7) Monoclonal antibody (Rituximab). (8) Immuno-suppressive drugs.

Surgery: (1) Orbital decompression. (2) Strabismus surgery. (3) Lid lengthening. (4) Blepharoplasty.

Contraindication – Patients showing evidence of marked exophthalmos. The likelihood of such patients developing even more severe exophthalmos of the malignant type after surgery is great.

Advantages – (i) Cures a higher percentage of patients. (ii) Cures in a shorter time.

Disadvantages – (i) Greater risk to the patient. (ii) Expense of hospitalization. (iii) Interference with patient's work for a considerable time. (iv) Complications like laryngeal paralysis, tetany and hypoparathyroidism. (v) Permanent hypothyroidism.

Table 27: Precipitating factors of hyperthyroid crisis

• Thyroid surgery
• Radioiodine
• Withdrawal of antithyroid drugs
• Iodinated contrast agents
• Acute illness (e.g. stroke, infection, trauma, diabetic ketoacidosis)

Preparation for surgery – The antithyroid drug is stopped 2 weeks before operation and replaced by pot. iodide 60 mg tds which reduces the size and vascularity of the gland. An alternative method for patients who need surgery within a short period of time is propranolol 80 mg t.d.s. and pot. iodide 60 mg t.d.s. for 10 days prior to surgery.

Management of Strategic Disorders in Thyrotoxicosis

Graves' disease in pregnancy – should not be managed by the block-replace regimen; insufficient thyroxine crosses the placenta to counter the effects of antithyroid drugs, resulting in foetal hypothyroidism. Instead the lowest possible dose of antithyroid drug should be used to maintain euthyroidism. Thyroidectomy is safe in the second trimester of pregnancy. If available, propylthiouracil should be used in early gestation because of the association of rare cases of fetal aplasia cutis and other defects, such as choanal atresia with carbimazole and methimazole. Because of its rare association with hepatotoxicity, propylthiouracil should be limited to the first trimester and then maternal therapy should be converted to methimazole (or carbimazole) at a ratio of 15–20 mg of propylthiouracil to 1 mg of Methimazole.

THYROID EMERGENCIES

Hyperthyroid Crisis (Thyroid Storm)

An uncommon, life-threatening exacerbation of thyrotoxicosis. See Table 27 for precipitating factors and Table 28 for the clinical features of hyperthyroid crisis.

Treatment

- Carbimazole 300 mg or propylthiouracil 600 mg loading dose, then 100 mg or 200 mg 6-hourly
- Stable iodine (e.g. Lugol's iodine or sodium ipodate 500 mg p.o. 1 hr. later)
- Propranolol 60 mg every 6 hours (Caution with complicating cardiac failure) or dexamethasone 8 mg orally od. If β-adrenergic blocking agents labetalol or esmolol are contraindicated, diltiazem may be used to slow the heart.

Table 28: Clinical features of hyperthyroid crisis

• Severe thyrotoxicosis
• Cardiac – Marked tachycardia, conduction disturbances such as AV blocks
• Cerebral: Delirium, seizure, coma
• GI: Vomiting, diarrhoea, abdominal pain, jaundice
• Fever

Table 29: Causes of hypothyroidism

Primary hypothyroidism (95% of cases)	*Secondary hypothyroidism (5% of cases)*	*Other causes*
Idiopathic Hashimoto's thyroiditis Irradiation of thyroid subsequent to Graves' disease Surgical removal of the thyroid Late stage invasive fibrous thyroiditis Iodine deficiency	Pituitary or hypothalamic neoplasms Congenital hypothyroidism Pituitary necrosis (Sheehan's syndrome)	Drug therapy (e.g. amiodarone, lithium, interferon) Infiltrative diseases (e.g. sarcoidosis, amyloidosis, scleroderma, hemochromatosis)

- Supportive measures (Dexamethasone, i.v. fluids, cooling)
- Treatment of precipitating cause

HYPOTHYROIDISM

Clinical condition resulting from reduced production of thyroid hormone. When the hypothyroidism is of severe degree and of long-standing, it is seen as myxoedema which is characterised by deposition of mucinous material (hyaluronic acid and mucopolysaccharides) causing swelling of skin and of subcutaneous tissues. The cause may be *primary thyroid disease*, or less commonly, disease of the pituitary or hypothalamus (*secondary hypothyroidism*) (Table 29).

Clinical Features

Onset – Insidious with physical, mental and metabolic processes below normal (Table 30).

A thyroid enlargement is usually made out by its movement on swallowing which will be lost only by a large impacted goiter, or by a rare case of invasive carcinoma or Riedel's thyroiditis.

Investigations

1. *Thyroid function tests* –

- Reduction in free and total T_4, and rise in serum TSH (usually more than 15–20 mU/L) indicates primary hypothyroidism.
- Elevated serum TSH with normal serum T_4 is termed 'subclinical' hypothyroidism.

  Note: Measurement of serum free or total T_3 is usually unhelpful, since T_3 may be only slightly reduced, because of increased peripheral conversion of T_4 to T_3.
- Reduction in free and total T_4, with TSH level within or below normal range, suggests secondary hypothyroidism.

Table 30: Clinical features of hypothyroidism

General
- Tiredness, somnolence
- Weight gain
- Cold intolerance
- Goiter
- Hyperlipidaemia

Skin and subcutaneous tissues
- Coarse dry skin
- Puffiness of face with malar flush
- Baggy eyelids
- Myxoedema – Swollen oedematous appearance of supraclavicular regions, neck, back of hands and feet
- Minimal sweating
- Alopecia
- Vitiligo
- Carotinaemia
- Erythema ab igne

Cardiovascular/Respiratory
- Bradycardia
- Angina
- Cardiac failure
- Pericardial effusions
- Pleural effusions

Psychiatric features
- Depression (myxoedema madness)
- Psychosis

Neuromuscular
- Aches and pains
- Carpal tunnel syndrome
- Cerebellar ataxia
- Myalgia and muscle stiffness
- Hoarseness
- Deafness of perceptive type
- Delayed relaxation of reflexes

Contd...

Contd...

Gastrointestinal –
• Constipation
• Ileus
• Ascites
Hematological –
• Iron deficiency anaemia (due to blood loss from menorrhagia).
• Macrocytic anaemia (due to associated vitamin B12 deficiency)
• Pernicious anaemia
• Normochromic, normocytic anaemia (most common) which may respond to thyroxine alone.
Reproductive system –
• Infertility
• Menorrhagia
• Hyperprolactianaemia and galactorrhoea
• Impotence
Developmental –
• Growth retardation
• Mental retardation
• Delayed puberty

2. *Serum cholesterol* – Elevated in primary thyroid failure. A fall in serum cholesterol level of more than 50 mg/dL in response to thyroxine treatment is good retrospective evidence of primary thyroid failure.
3. *ECG* – Bradycardia, low voltage complexes and flattened or inverted T waves. Marked improvement occurs with thyroxine treatment.
4. *Thyroid antibodies* – (Refer)

Iodine-deficient hypothyroidism – Most iodine deficient individuals have a goiter but are euthyroid with normal or elevated serum TSH.

Cretinism – Severe maternal iodine deficiency leading to goiter and hypothyroidism is associated with – (a) *Neurological cretinism:* Mental retardation after birth, which is not improved by iodine or thyroid supplementation either in pregnancy or neonatal life. (b) *Myxoedematous cretinism:* Iodine deficiency in late pregnancy results in neonatal hypothyroidism, which predominantly affects somatic development leading to marked growth retardation, and responds to iodine supplementation or thyroxine.

Management

Initiating replacement therapy

Table 31 gives dosages to initiate thyroxine replacement therapy and Table 32 gives conditions requiring increase in thyroxine dosage.

Table 31: Initiating thyroxine replacement therapy

Patient	*Thyroxine therapy*
Healthy adult patients with hypothyroidism	Thyroxine 1.6 µg/kg/d
Elderly children	1 µg/kg/d may require upto 4 µg/kg/d
Young patients without risk factors for cardiovascular disease	Levothyroxine 0.075 mg/d to be titrated against serum TSH levels with small gradual increments
Patients at risk of cardiovascular compromise	Thyroid replacement at 0.025 mg/d, gradually increased by 0.025 to 0.50 every 4–6 weeks till TSH levels are normalized

Table 32: Conditions requiring increase in thyroxine dosage

Pregnancy: Foetal requirement for T4	
Drugs:	
Increased clearance of T4	Rifampicin
	Phenytoin
	Carbamazepine
Decreased absorption of T4	Cholestyramine
	Sucralfate
	Aluminium hydroxide
	Ferrous sulphate

Clinical Response

The earliest is usually diuresis and weight loss is usually minimal and late. Other features which improve are appetite, constipation, hoarseness of voice, and much later cold intolerance and fatigue.

Monitoring therapy – The objective of T_4 therapy is to restore serum T_4 and TSH to normal levels. In most patients dose requirements of T_4 do not change but pregnancy and some drugs, e.g. rifampicin, phenytoin, carbamazepine (increased clearance of thyroxine), and cholestyramine, sucralfate, aluminium hydroxide, ferrous sulphate (decreased absorption of thyroxine) may necessitate a dose increase.

Duration of therapy – Mild hypothyroidism occurring within the first 6 months after therapy for hyperthyroidism, or diagnosis of subacute or silent thyroiditis, may be temporary. If symptoms are sufficiently severe, T4 can be given for 6 months and then stopped for 6 weeks so that serum TSH can be measured. For hypothyroidism in other circumstances T_4 therapy is lifelong.

Special Situations

Ischaemic heart disease – T_4 should be started on a low dose (25 µg daily or on alternate days) to avoid precipitating a worsening angina, or myocardial infarction. The dose can be increased every 4 weeks until euthyroidism is achieved.

'Subclinical' hypothyroidism – Elevated serum TSH with normal T_4 levels is seen in patients treated for hyperthyroidism, and also occurs spontaneously, particularly in the elderly. The slowly progressive nature of thyroid failure in these patients, particularly those who have received radioiodine or who are thyroid antibody-positive, require T_4.

Pregnancy – In patient on thyroxine replacement therapy, the mean increment in the required daily dose is 50 µg, which is usually by the end of the first trimester though may be delayed as the 6th month in some. The levothyroxine dose may need to be increased by up to 50% during pregnancy, with a goal TSH of less than 2.5 mlU/L during the first trimester and less than 3.0 mlU/L during the second and third trimesters.

Central hypothyroidism – Glucocorticoid replacement should be initiated prior to thyroxine replacement.

Drug interactions – With antacids and iron formulations concurrent use of these may reduce efficacy of Levothyroxine by binding and deleting or preventing absorption of calcium carbonate and ferrous sulphate from insoluble chelate and ferric thyroxine complex respectively. Hence these drugs should be taken at least 4 hours apart from levothyroxine.

Myxoedema coma –Severe life, threatening complication of hypothyroidism typically seen in the elderly and often precipitated by infection, therapy with sedative drugs or inadequate heating in cold weather. Cerebrovascular accidents, CHF, overuse of diuretics.

Cl. Fs. – Although coma does not occur in all patients, depression of the conscious level is common and majority of patients have hypothermia. Other features include hypotension, bradycardia, hyponatraemia and hypoventilation with hypoxia and hypercapnia.

Management

(a) Admission to ICU. (b) Ventilatory support for at least 24–48 hours with frequent measurement of atrial blood gases. (c) Endotracheal tube to be retained till patient fully conscious. (d) If hyponatraemia, fluid restriction and small volume of saline or dextrose saline, usually adequate. If serum sodium falls <120 mEg/L, hypertonic saline followed by IV frusemide to promote water diuresis may be needed. (e) Warmth should be carried out cautiously or else the resultant peripheral vasodilation may cause hypotension. (f) Hydrocortisone 50–100 µg to tackle the impaired adrenal reserve which may manifest when thyroxine therapy is initiated. (g) Thyroid hormone – T4 300-500 µg loading dose followed by 50–100 µg q6h for one or two days. Once patient has an improved sensorium and is accepting orally he/she can be shifted back to oral replacement therapy.

THYROIDITIS

Thyroiditis is a term indicating presence of thyroid inflammation, and thus comprises a large group of diverse inflammatory conditions. Table 33 gives etiological classification of thyroidirtis.

Acute Thyroiditis

Clinical features of acute thyroiditis are local pain and tenderness in the affected lobe or entire gland with dysphagia, fever, anterior neck pain. Radioiodine scanning shows "cold" suppurative area. FNab with staining and culture is diagnostic. Appropriate antibiotic therapy and drainage of abscess is the therapy.

Subacute Thyroiditis

Painful subacute thyroiditis often follows viral upper respiratory illness (mumps, coxsackie, influenza and adenovirus) and is the common cause of thyroid pain. Fever, dysphagia, fatigue, anxiety, sweat may occur. Thyroid is very tender, hard, mild to moderately enlarged and often nodular. Pain in neck is constant, after aggravated by neck movements. ESR and CRP are elevated, and thyroglobulin level is high. Doppler study reveals hypoechogenic glands. Subacute thyroiditis is usually self-limiting, euthyroidism is achieved in majority of cases over 6–12 months. *Tr.*

Table 33: Etiological classification

Acute
• Infective – Bacterial: Staphylo, Strepto, Enterobacter – Fungal: Aspergillus, Candida, Histoplasma, Pneumocystis – Radiation therapy – Drug-induced: Amiodarone
Subacute
• Infective – Viral or granulomatous thyroiditis – Mycobacterial infection – Silent thyroiditis (including postpartum thyroiditis)
Chronic
• Autoimmune: Focal thyroiditis, Hashimoto's thyroiditis, atrophic thyroiditis • Riedel's thyroiditis
• Infective – Parasitic: Echinococcosis, cysticercosis Traumatic: After palpation

NSAIDs for mild to moderate pain, in severe cases. Prednisolone upto 40 mg/d. If hypothyroid state is prolonged, thyroxine 50–100 µg daily.

Autoimmune Thyroid Disorder

AITD is the most common organ specific autoimmune disorder comprising Graves' disease, Hashimoto's thyroiditis, (goitrous), atrophic thyroiditis, silent thyroiditis and thyroid associated ophthalmopathy. Middle aged women and men are commonly affected.

Cl. Fs.: Depends upon type and stages of the disease. Hashimoto's thyroiditis presents with small to large firm and painless goiter. Patients slowly develop progressive hypothyroidism, some eventually become hypothyroid. The disease is associated with other autoimmune diseases including pernicious anaemia. Graves' disease has also been mentioned. Thyroid lymphoma is a rare complication of chronic autoimmune thyroiditis.

Diagnosis: CFD is helpful for semiquantitative measurement of blood flow to thyroid gland.

Treatment: (i) Hashimoto's thyroiditis. FNAC is useful, L-thyroxine replacement. (ii) Graves' disease - Antithyroid drugs, propranolol. (iii) Painless postpartum thyroiditis. Thyrotoxic phase can be treated with beta-blockers, during breast feeding. Iodine^{131} is contraindicated. By using technetium pertechnate, interruption of breast feeding for only 24 hours.

Drugs: known to provoke autoimmune or destructive inflammatory thyroiditis are lithium, amiodarone, interferon, interleukin-2 and sunitinib.

Post-partum thyroiditis. Painless lymphocytic thyroiditis occurs in up to 10% of women, post-partum. This is an inflammatory autoimmune disorder in which lymphocytic infiltration results in thyroid destruction and leads to transient mild thyrotoxicosis as thyroid hormone stores are released from the damaged thyroid. As the gland becomes depleted of thyroid hormone, progression to hypothyroidism occurs. Thyroid function returns to normal within 12-18 months in majority of cases.

Painful subacute thyroiditis, the most common cause of thyroid pain, is a self-limiting inflammatory disorder of possible viral etiology. Patients typically present with fever and severe neck pain or swelling or both. About half will describe symptoms of thyrotoxicosis. After several weeks, most patients will develop hypothyroidism. Thyroid function eventually returns to normal in almost all patients. ESR and C-reactive protein are elevated in painful subacute thyroiditis.

Riedel's thyroiditis is rare and occurs primarily in middle aged women. The etiology is uncertain and the condition is characterised by fibrosis of thyroid gland and adjacent structures. Symptoms develop insidiously and are due mainly to compression of adjacent structures including trachea, oesophagus and recurrent laryngeal nerve. The thyroid gland is moderately enlarged, stony hard and usually asymmetrical, severe hypothyroidism may occur. Surgery may be necessary to preserve tracheal and oesophageal function. Tamoxifen may also be beneficial. There is an association between Riedel's thyroiditis and IgG4-related systemic disease causing idiopathic fibrosis at other sites (retroperitoneum, mediastinum, biliary tree, lung and orbit).

Hashimoto's thyroiditis – An autoimmune disorder which typically affects middle-aged and elderly women. *Cl. Fs.* – Presentation is with goiter, hypothyroidism or both. *Associated conditions* – include vitiligo, pernicious anaemia, type 1 diabetes mellitus, Addison's disease, and premature ovarian failure. Increased incidence is also found with Down's or Turner's syndrome.

4. THYROID GOITER

A goiter is an enlargement of the thyroid gland, and may be symmetrical, asymmetrical or nodular. See Table 34 for WHO classification of goiter and Table 35 for causes of goiter.

HISTORY

- Long-standing goiter suggests benign disease, unless there has been recent rapid development.
- Ingestion of drugs with goitrogenic action (lithium, antithyroid drugs, iodine).
- Exposure to radiation (particularly in childhood) is a risk for both benign and malignant nodular thyroid disease.

Table 34: WHO classification of goiter

Grade	*Description*
0	No goiter
1A	Goiter detectable by palpation alone
1B	Goiter palpable and visible only when the neck is fully extended
2	Goiter visible with the neck in normal position
3	Very large goiter visible at 10 meters

Table 35: Causes of goiter

Diffuse goiter
• Simple, non-toxic
• Grave's disease
• Hashimoto's thyroiditis
• Subacute thyroiditis
• Painless (silent) thyroiditis
• Thyroid lymphoma
Single nodule
• Adenoma
• Carcinoma
Multiple nodules
• Multinodular goiter
• Hashimoto's thyroiditis

- Age of the patient: Thyroid nodules are uncommon in childhood. There may be increased risk of cancer in nodules that develop after the age of 65 years.
- Family history of goiter may suggest autoimmune thyroiditis.
- Pain and tenderness usually suggest subacute thyroiditis or hemorrhage into a cyst.

EXAMINATION

- **Size of the goiter**
- Other features – whether it is diffuse or nodular, firm or hard, tender or painless and its mobility.
- Vascular thrill and systolic bruit suggest hyperthyroidism
- Hoarseness or dyspnoea are more likely to be due to local invasion by malignancy rather than multinodular goiter
- Presence or absence of cervical lymphadenopathy.

Table 36 gives the functional status of thyroid goiter.

Table 36: Functional status of thyroid goiter

Euthyroid goiter	*Hypothyroid goiter*	*Hyperthyroid goiter*
Iodine deficiency goiter	Iodine deficiency goiter	Permanent
Autoimmune thyroiditis	Autoimmune thyroiditis	Graves' disease
Subacute thyroiditis	Hashimoto's thyroiditis	Toxic MNG
Postpartum thyroiditis	Subacute thyroiditis	Toxic adenoma
Familial goiter	Postpartum thyroiditis	Iodine induced
Malignancy	Familial (Congenital) goiter	Transient
Goitrogens	(Dyshormonogenesis)	Subacute thyroiditis
Idiopathic	Goitrogens, antithyroid drugs	Postpartum thyroiditis
		Chronic thyroiditis

INVESTIGATIONS

1. Biochemical tests

Iodine deficiency disorder (IDD) – Severity of IDD can be defined as follows depending on urinary excretion of iodine and prevalence of goiter –

- Mild IDD – Goiter prevalence of 5–20% with mean urinary iodide levels > 50 mg/g of creatinine
- Moderate IDD – Goiter presence of 30%, some hypothyroidism and mean urinary iodide levels in the range of 25-50 mg/g of creatinine
- Severe IDD – Goiter prevalence> 30%, endemic cretinism (1–10%), and mean urinary iodide levels < 25 μγ/g of creatinine

Circulating concentrations of thyroid hormone and TSH – to exclude hyperthyroidism and hypothyroidism.

Serum calcitonin – Calcitonin secretion is increased in medullary thyroid cancer.

2. Immunological tests

- *Circulating thyroid antibodies* (thyroglobulin and thyroid peroxidase) suggest an autoimmune basis for the goiter and are associated with increased risk of future hypothyroidism
- *Serum concentrations of thyroglobulin* are raised in patients with benign or malignant nodules, and is hence of no value in initial assessment of nodular thyroid disease

3. Imaging

- *Thyroid scintiscanning* – Technetium- 99m pertechnate is the most commonly used radionuclide. Pertechnate ions are trapped by thyroid. Most thyroid malignancies do not concentrate radioisotopes (and thus appear 'cold'), but < 20% of these nodules are caused by cancer, the remaining 80% result from colloid nodules, hemorrhages, cysts or inflammatory lesions (e.g. Hashimoto's thyroiditis). Radionuclide imaging may reveal multifocal abnormalities in patients thought clinically to have a solitary nodule.
- *Ultrasonography* – High resolution ultrasonography can detect lesions of the thyroid as small as 1 mm in diameter. It distinguishes solid from cystic lesions.

- *CT or MRI of neck and thoracic inlet* – for evaluating thyroid size and mediastinal extension of thyroid masses.

4. Fine-needle aspiration biopsy

Obtains thyroid tissue for direct cytological examination and is the optimal initial approach to investigation of a thyroid nodule. Lymphocytic infiltration, obliteration of thyroid follicles, fibrosis and presence of Askanazy cells suggest Hashimoto's thyroiditis; hyperplastic thyroid follicles with fire flare Graves's disease, benign cells adenoma and frankly malignant cells malignancy, lymphoma or metastatic neoplasm.

5. PARATHYROID DISORDERS

HYPOCALCAEMIC DISORDERS

The clinical presentation of hypocalcaemia ranges from an asymptomatic biochemical abnormality to a severe life-threatening condition. Normal serum calcium is 2.15–2.65 mmol/ liter. See Table 37 for the causes of hypocalcaemia.

Table 37: Causes of hypocalcaemia

1. *Parathyroid-related disorders*
Absence of parathyroid gland or parathyroid hormone
• Congenital
– DI George syndrome
– X-linked or autosomal inherited hypoparathyroidism
– Autoimmune polyglandular syn. type 1
– PTH gene mutations
• Post-surgical
• Infiltrative disorders
– Hemochromatosis
– Wilson's disease
– Metastases
• After radioactive iodine thyroid ablation
• Impaired secretion of PTH
– Hypomagnesaemia
– Pseudohypoparathyroidism
2. Vitamin D-related disorders
• *Vitamin D deficiency*
• Dietary deficiency
• Impaired absorption
• Increased loss
Contd...

Contd...
– Impaired enterohepatic recirculation
– Anticonvulsant medications
• Impaired 25-hydroxylation
– Liver disease
– Isoniazid
• Impaired 1α-hydroxylation
– Kidney failure
• Vitamin D-dependent rickets type I
• Oncogenic osteomalacia
• Target organ resistance
– Vitamin D-dependent rickets type II
– Phenytoin
3. Miscellaneous causes
• Excessive deposition into the skeleton
– Osteoblastic malignancies
– Hungry bone syndrome
• Chelation
– Foscarnet
– Phosphate infusion
– Citrated blood products infusion
– Infusion of EDTA-containing contrast reagents
– Fluoride
• Neonatal hypocalcaemia
– Asphyxia
– Prematurity
– Diabetic mother
– Hyperparathyroid mother
• HIV infection
– Drug therapy
– Vitamin D deficiency
– Hypomagnesaemia
– Impaired PTH responsiveness
• Severe illness
– Pancreatitis
– Toxic shock syndrome
– Patients in ICUs

DiGeorge syndrome: It arises from development failure of derivatives of 3rd and 4th pharyngeal pouches, causing agenesis or hypoplasia of thymus (immunodeficiency) and parathyroids (hypocalcaemia), cleft lip and palate, and congenital heart disease.

Clinical Features of Hypocalcaemic Neuromuscular Irritability

- Paraesthesia, usually of fingers, toes and circumoral regions.
- Tetany (Table 38), carpopedal spasm, muscle cramps
- Seizures of all types (focal or petit mal, grand mal, or syncope)
- Laryngospasm or grand mal seizures in severe hypocalcaemia during acute falls in serum Ca
- Bronchospasm
- Prolonged QT interval

Latent Tetany

1. *Trousseau's sign* – Carpal spasm produced by compressing the upper arm with a sphygmomanometer cuff to 20 mm Hg above the systolic pressure for 3 minutes.
2. *Chvostek's sign* – Contraction of facial muscles by tapping over the facial nerve in front of the lobe of the ear.
3. *Erb's sign* – Muscles show increased excitability to galvanic stimulation.

Investigations and Diagnosis

Hypoparathyroidism – Serum calcium low, phosphate high and PTH undetectable. Renal function and concentrations of 25-hydroxy and 25-dihydroxy metabolites of vitamin D are normal.

Chronic kidney failure – Low serum calcium, high phosphate, alkaline phosphatase, creatinine and PTH. Normal 25-hydroxyvitamin D_3 and low 1,25-dihydroxyvitamin D_3.

Table 38: Causes of tetany

1. *Hypocalcaemia*
– Hypoparathyroiditis
– Malabsorption
– Osteomalacia
– Chronic kidney failure
2. *Due to alkalosis*
– Frequent vomiting (of gastric juice)
– Intake of alkalis
– Hyperventilation
– Primary hyperaldosteronism
3. *Due to hypomagnesaemia*

Vitamin D-deficiency osteomalacia – Low serum calcium and phosphate, raised alkaline phosphatase and PTH, normal renal function and low 25-hydroxyvitamin D_3.

Management of Acute Hypocalcaemia

Indications

- Symptomatic patients (e.g. with tetany)
- Asymptomatic patients with serum calcium < 1.90 mmol/L, who may be at high risk of developing complications.

Therapy

Calcium gluconate 10ml 10% iv, diluted in 50ml 5% dextrose by slow infusion (> 5 minutes), to be repeated as required to control symptoms.

- For continuing hypocalcaemia – Dilute 10 ampoules of calcium gluconate 10 ml 10% in 1 liter 5% dextrose. Infusion at 50 ml/hour and titrate to maintain serum calcium in the low range. If associated hypomagnesaemia, it must be corrected first. Vitamin D orally if hypocalcaemia is likely to persist.

Management of Persistent Hypocalcaemia

1. Supplemental calcium 10-20 mmol b.d.
2. Vitamin D preparations: (a) Vitamin D_3 (cholecalciferol or vitamin D_2 (ergocalciferol) 25,000-100,000 units (1.25–5 mg/day). (b) Alfacalcidol (l α -hydroxycalciferol) 0.25–1.0 µg/day. (c) Calcitriol (1, 25-dihydroxycholecalciferol) 0.25–2.0 µg/day drug of choice.

CHRONIC HYPOPARATHYROIDISM

Clinical Features

1. *Ectodermal changes* – Nails become brittle, ridges develop and may fall off. Permanent teeth hypoplastic and transversely ridged if disease commences before tenth year. Vesicular or eczematous eruptions may occur on skin. Fissures at angles of mouth. Hair tend to become dry and sparse. Cataracts common. Systemic moniliasis.
2. *Mental symptoms* – Varying from minor disturbances to major psychoses. Electroencephalographic abnormalities may precede development of epilepsy and psychological symptoms.
3. *Diagnostic changes in serum Ca,P and alkaline phosphatase.*

4. *Raised intracranial tension and papilloedema* – may occur, return to normal with correction of hypocalcaemia.
5. *Intracranial calcification* – seen on X-ray in region of basal ganglia as symmetrical punctate opacities.
6. ECG – QT interval prolonged.

Pseudohypoparathyroidism – is characterized by hypocalcaemia caused by PTH resistance. Three major variants are recognised on the basis of biochemical and somatic features – PHP type Ia, PHP type Ib, pseudo- pseudohypoparathyroidism (PPHP) and PHP II.

Patients with PHPIa exhibit PTH resistance (hypocalcaemia, hyperphosphataemia, elevated serum PTH, absence of increase in serum and urinary cyclic AMP and urinary phosphate after iv PTH infusion). Associated features of Albright's hereditary osteodystrophy (AHO) namely short stature, obesity, subcutaneous calcification, mental retardation, round facies and brachydactyly.

PHP1β – PTH resistance but no somatic features of AHO.

PPHP – Somatic features of AHO in absence of any evidence of PTH resistance.

PHP-II refers to patients with hypocalcemia and hyperphosphatemia, who have a normal urinary cAMP but an impaired urinary phosphaturic response to PTH.

HYPERCALCAEMIA

See Table 39 for the causes of hypercalcaemia.

Parathyroid-dependent hypercalcaemia – Abnormal parathyroid glands are associated with hypercalcaemia in three distinct settings: (a) Primary hyperparathyroidism. (b) Familial hypercalcaemic hypercalcaemia (FHH) and (c) Lithium-induced hypercalcaemia.

Clinical features: Most patients with primary hyperparathyroidism present with hypercalcaemia, and as the serum calcium increases, the likelihood of clinical symptoms also increases.

1. *Age and Sex* – Parathyroid tumours are 3 times more common in women than in men. Incidence increases with age, most common in post-menopausal women.
2. *Onset* – (i) Usually gradual. Increasing asthenia, bone pains or swelling of bone. (ii) Rarely sudden, e.g. fracture or renal colic.
3. *Hypercalcaemic features* – Muscular weakness, fatigue. Constipation, loss of weight, anorexia, nausea and sometimes vomiting, malaise. Conjunctival flare, irritable eyes. Drowsiness and confusion.

Table 39: Causes of hypercalcaemia

1. Parathyroid dependent hypercalcaemia
• Primary hyperparathyroidism
• Tertiary hyperparathyroidism
• Familial hypocalciuric hypercalcaemia
• Lithium associated hypercalcaemia
• Antagonistic antibodies to calcium sensing receptor
2. Parathyroid independent hypercalcaemia
• l Neoplasms
– PTHrP dependent
– Other humoral syndromes
– Metastases
• PTHrP excess (non-neoplastic)
• Excess vitamin D
– Excess ingestion
– Granulomatous disease
– Williams' syndrome
• Thyrotoxicosis
• Adrenal insufficiency
– Kidney failure
– AKF
– CKF with aplastic bone disease
• Immobilization
• Drugs
– Vitamin A intoxication
– Milk-alkali syndrome
– Thiazide diuretics
– Theophylline

4. *Renal manifestations* –
   (a) Due to chemical changes in urine –polydipsia and polyuria.
   (b) Due to nephrolithiasis – haematuria and renal colic.
   (c) Due to nephrocalcinosis – chronic nephritis, hypertension.
5. *Skeletal involvement* – is due to generalized increase in osteoblastic bone resorption and increased osteoblastic activity. Radiographic features of hyperparathyroidism are given in Table 40.
6. *Metastatic calcification* – Calcareous deposits in pericardium, myocardium or lungs may produce dyspnoea and tachycardia, and in the muscles pain and tenderness. Corneal calcification may occur.

Table 40: Radiographic features of hyperparathyroidism

- Generalized demineralization of bone with coarsening of the trabecular pattern
- Subperiosteal resorption, most evident in phalanges of the hands
- Bone cysts, usually multiple, tend to occur in central medullary portions of metacarpals, ribs or pelvis and can expand into and disrupt overlying cortex
- Osteoclastomas (brown tumors) found most often in trabecular portions of the jaw, long bones and ribs
- Pathological fractures
- Skull can show a finely mottled 'salt-and-pepper' appearance with loss of definition of inner and outer cortices
- Dental radiographs show erosion or disappearance of lamina due to subperiosteal resorption

Table 41: Biochemical features

Serum	*Normal*	*Hyperparathyroidism*
Calcium	Total 9–11 mg. Ionized 5.9–6.5 mg.	More than 11 mg. 6.7-9.5 mg.
Phosphorus	2.5–4.5 mg.	Lowered or normal
Alkaline phosphatase	Females: 5.6 ± 1.8 units Males: 7.6 ± 1.9 units	About 20 units (if associated active bone disease)
PTH	<1 ng/mL	Usually twice normal

Markers of bone formation (e.g. osteocalcin) and bone resorption (e.g. urinary calcium, hydroxypyridinium) in upper range of normal.

7. *Gastrointestinal features* – Peptic ulceration is common.
8. *Renal functional abnormalities* – that range from renal concentrating ability to end-stage kidney failure.
9. *Multiple endocrine neoplasia* – are commonly associated with presence of parathyroid adenoma or hyperplasia. Presence of hypercalcaemia with labile hypertension and neurofibroma are suggestive.
10. *Unusual presentation* – Occasionally psychosis. Rarely acute pancreatitis.

Diagnosis

1. *Biochemical features: (Table 41).*
2. *Radiographs* of bony changes have been already described.
3. *Hydrocortisone suppression test* – 120 mg. hydrocortisone or 10 mg. prednisolone 8-hourly for 10 days. In patients with primary hyperparathyroidism the plasma calcium level does not usually fall, in most other hypercalcaemic conditions there is marked fall.

Table 42: Differentiation between primary hyperparathyroidism and malignancy-related hypercalcaemia

	Primary	*Malignancy-related*
Presentation	Typically, as asymptomatic or detected on biochemical screening for other reasons	Diagnosis is made in more advanced stages of underlying disease
Biochemical features	PTH elevated	PTH suppressed Elevated PTHrp (parathyroid hormone-related protein)

Localization of Parathyroid Adenoma

(a) *Scan* – After imaging during successive injections of Thallium-201 (taken up by both thyroid and parathyroid), followed by technetium-99 m (taken up only by thyroid), a computer subtracts one image from the other leaving a parathyroid image if an adenoma is present.

(b) *Ultrasound*– CT scanning is not successful in adenomas less than 0.5 cm in diameter. Ultrasound technique using 10 megahertz waves is more effective.

(c) *Bone mass* – Measured by dual-energy X-ray absorptiometry (DXA) useful in assessing presence or extent of skeletal involvement.

Differential Diagnosis

1. **Differentiation from other causes of hypercalcaemia**

Primary hyperparathyroidism

- Sporadic (adenoma, hyperplasia or carcinoma)
- Familial
  - Isolated
  - Cystic
  - Multiple endocrine neoplasia type 1 or 2

Malignancy

- Parathyroid hormone - related peptide
- Excess production of 1, 25-dihydroxy vitamin D_3
- Other factors (cytokine, growth factors)

Note: The above two are responsible for 90% of cases

See Table 42 for differences between primary hyperparathyroidism and malignancy-related hypercalcaemia.

2. **Differential diagnosis of polyuria (and polydipsia).**
3. **Differentiation from other skeletal diseases –** (a) *Osteoporosis* – Generalized decalcification especially of vertebrae in post-menopausal women, old age, enforced disuse, corticosteroid therapy. Plasma calcium

phosphorus and alkaline phosphatase normal. (b) *Rickets* – Wide and irregular epiphyseal line. Ill-nourished children. (c) *Osteomalacia* – Generalized decalcification in young women on inadequate diet. Plasma calcium and alkaline phosphatase show diagnostic changes. (d) *Osteogenesis imperfecta* – Bones thin, not obviously decalcified. Familial. China-blue sclerotics, otosclerosis, spontaneous fractures. (e) *Paget's disease* – Patchy decalcification with new bone formation. Changes usually confined to skull, spine, pelvis, femurs, and tibiae. (f) *Multiple myeloma* – General decalcification with punched out areas, Bence Jones proteinuria. Myeloma cells in bone marrow. (g) *Metastases* – Patchy distribution, presence of primary growth.

4. **Milk-Alkali syndrome** – The triad of hypercalcaemia, metabolic alkalosis and kidney failure can result from huge ingestion of calcium and absorbable alkali like calcium carbonate. Immobilization can lead to bone resorption sufficient to cause hypercalcaemia.
5. **Kidney failure** – Following rhabdomyolysis, during the oliguric phase of kidney failure, severe hypercalcaemia can result from acute hyperphosphataemia and calcium deposition in muscle.
6. **Williams' syndrome** – in which valvular AS is associated with elfin facies and mental retardation, hypercalcaemia can occur transiently in first four years of life.
7. **Jansen's metaphyseal chondrodysplasia** – A rare disease in which children present with short stature and hypercalcaemia.

Management

Parathyroid surgery

Indications

- Serum calcium >1 mg/dL above upper limit of normal
- Marked hypercalciuria (>400 mg/day)
- Any overt manifestation of primary hyperparathyroidism (e.g. kidney stones, nephrocalcinosis, osteitis fibrosa cystica, classical neuromuscular disease, symptomatic or life-threatening hypercalcaemia)
- Creatinine clearance <70% of predicted (<60 mL/min)
- Bone mineral density low (T score <2.5 of any site)
- Uncertain prospects for adequate medical monitoring
- Age <50 years

Medical monitoring – (a) Serum calcium should be checked twice yearly, and urinary calcium and bone mass (particularly of the forearm) measured annually. (b) Patient should maintain an active lifestyle and avoid any prolonged period of immobilization or dehydration. (c) Dietary calcium should neither be severely restricted nor much promoted. (d) In post-menopausal women, oestrogen therapy to reduce serum calcium by about 0.5 mg/dL and to provide other benefits of hormone replacement. (e) Potent amino-substituted bisphosphonates such as alendronate are useful. (f) Administration of analogues of ligands that activate the calcium-sensing receptor, leading to an increase in parathyroid cell calcium levels and suppression of further PTH production is another approach to medical management.

Table 43: Management of hypercalcaemia

Therapy	*Dosage*
Rehydration	2–4 L/day normal saline drip
Furosemide	20–40 mg iv after rehydration 12–24 hrly
Pamidronate	60–90 mg iv over 2–4 hr once
Zoledronate	4 mg iv over 15–30 min. once
Calcitonin	4–8 IU/kg SC q 12–24hr
Gallium nitrate	200 mg/m2 iv over 24 hr x 1–5 doses
Plicamycin	15–25 µg/kg iv over 4-6 hr 1–5 doses
Glucocorticoids	200–300 mg hydrocortisone iv over 4–6hr x 3–5 days
Dialysis	

PARATHYROID CRISIS

Severe hypercalcaemia (Serum calcium >12 mg/dL)
Cl.Fs – Fatigue, weakness, lethargy, confusion, anorexia, nausea, abdominal pain and constipation. Also polyuria, nocturia and polydipsia. Cardiac arrhythmias particularly bradyarrhythmias and heart block.

Management

See Table 43.

6. THE ADRENALS

ADRENOCORTICAL HYPOFUNCTION

Acute Adrenocortical Insufficiency

Causes – May occur in – (a) Adrenalectomized patients. (b) Patients with Addison's disease with inadequate substitution therapy especially with vomiting, diarrhoea, surgical operation, parturition or intercurrent infection. (c) Rarely with meningococcal septicaemia (Waterhouse-Friderichsen syndrome).

Clinical features – Sudden onset with fall of blood pressure, cold and cyanosed extremities, nausea, vomiting and diarrhoea, stupor and terminal coma.

Management – Hydrocortisone 100 mg i.v or i.m is given and a drip started. One liter 0.9% saline is administered in 30–60 min, and several liters of saline, with 5% dextrose if hypoglycaemia. Hydrocortisone 100 mg i.m. is given 6-hourly in the acute phase. Oral medication can be restarted after 24 hours and reduced to maintenance dose over 3–4 days.

ADDISON'S DISEASE

Addison's disease is primary adrenal failure.

Causes

Common

- Autoimmune adrenalitis
- Infections – Tuberculosis. Cytomegalovirus and fungal infections associated with AIDS.
- Tumours – Metastatic disease (notably from breast)
- Inherited disorders – e.g. adrenoleucodystrophies and familial isolated glucocorticoid deficiency.

Rare – Secondary deposits, granulomatous disease, amyloidosis, haemochromatosis, fungal disease (e.g. histoplasmosis); congenital adrenal hyperplasia, meningococcal septicaemia, haemorrhage into adrenals, e.g. in new born or as complication of anticoagulant therapy, adrenal vein thrombosis after trauma or adrenal venography. Drugs, e.g. rifampicin, ethionamide, ketoconazole.

Clinical Features

Onset – usually insidious. Rarely first manifestation may be acute crisis.

1. *Pigmentation of skin and mucous membranes* – Varieties – (a) Bluish black discolouration, or brownish patches or streaks on lips, gums, inside of cheeks and posterior aspect of the palate almost pathognomonic. Rectal and vaginal surfaces also involved. (b) A diffuse tan over the non-exposed as well as exposed portions of the body. (c) Hyperpigmentation of extensor surfaces, pressure points and scars, e.g. face, neck, dorsum of hands and forearms, waist line, knuckles and ankles. Palms and soles escape pigmentation except for the creases at the interphalangeal joints. (d) Multiple black freckles especially on the forehead, face, neck, shoulders and arms. (e) Areas of vitiligo or leukodermic type of pigmentation.
2. *Gastrointestinal symptoms* – Anorexia, often with nausea and vomiting. Constipation with intermittent diarrhoea. Salt craving. Abdominal pain. Irritation of the diaphragm by tuberculous adrenal may produce shoulder pain.
3. *Cardio-vascular system* – Postural hypotension. Faintness may result on assuming erect position. Sometimes dyspnoea. Heart sounds feeble.
4. *Muscular system* – Muscular weakness, and wasting with creatinuria. Sometimes cramps in muscles.
5. *Mental and nervous* – Lassitude and muscle weakness are invariable and the first symptom to appear in majority of cases. Loss of memory, drowsiness. Sometimes periods of restlessness, irritability and insomnia. Negativism and pessimism in chronic cases.
6. *Genital system* – Impotence and amenorrhoea. Symptoms may be aggravated at the time of menstruation or menopause.
7. *Kidneys* – In a crisis, and to a less extent in subacute phases of the disease, kidney function is severely impaired, the excretion of urine is diminished and it contains granular casts and albumin, and the blood urea and creatinine rise above normal.
8. *Miscellaneous* – Subnormal temperature, anaemia. Loss of body hair (axillary and pubic) in females.
9. *Other autoimmune disease* – Clinical features of other associated autoimmune disease such as vitiligo, thyroiditis, with or without hypothyroidism; pernicious anaemia, hypoparathyroidism, insulin-dependent diabetes mellitus, mucocutaneous candidosis.

Table 44 gives pathogenesis of symptoms of adrenocortical insufficiency.

Addisonian crisis – An acute phase of the disorder in which the patient presents with severe collapse, shock, vomiting, dehydration, hypotension, profound weakness and hypoglycaemia. *Causes* – Usually severe or

Table 44: Pathogenesis of symptoms of adrenocortical insufficiency

1. Increased secretion of ACTH	Pigmentation of skin in areas exposed to light, in oral mucosa, gums
2. Deficiency of adrenal cortisol secretions – Cortisol – Aldosterone – Androgens	Asthenia Pigmentation of points of pressure (e.g. elbows and mucus membrane, e.g. genital regions, mouth) Anorexia, nausea Weight loss Decreased tolerance to stressful situation Hypotension, postural syncope Diminished axillary and pubic hair growth in females

long-standing hypoadrenalism, or precipitated by intercurrent illness (e.g. pneumonia or other infections), severe diarrhoea, vomiting or major surgery. An intercurrent infection is a predisposing factor but at times there may be no precipitating cause. Extra exertion, anxiety, reduction in dosage of corticosteroids are other causes.

Warning signs – Yawning, hiccough, photophobia, increased sensitivity to cold or actual shivering with the patient curling himself up beneath blankets, and irritability.

SECONDARY ADRENOCORTICAL INSUFFICIENCY

Due to pituitary or hypothalamic diseases such as tumours, infarction, trauma, granuloma or necrosis. It can also be induced by corticosteroid therapy which suppresses corticotrophin releasing hormone (CRH). Symptoms and signs identical to Addison's disease except absence of pigmentation. Features associated with hypotension are unusual since aldosterone secretion is maintained despite absence of ACTH.

Investigations

A. Of Addison's disease

1. Plasma cortisol level – measured at 9 am < 50 nmol/liter confirms diagnosis of adrenocortical insufficiency.
2. Plasma ACTH level – High (> 80 ng/liter).
3. Synacthen tests –
   (a) *Short Synacthen test* – Following injection of Synacthen 250 mg i.m., cortisol levels are sampled at 30 minutes and 1 hour. If these fail to rise above 550 nmol/liter, or fail to increase by more than 230 nmol/liter, the test is positive for adrenal failure.
   (b) *Depot Synacthen test* – If Addison's disease is strongly suspected and/or result of short Synacthen test is abnormal or equivocal. Take blood for plasma cortisol (preferably at 9 am), then give 1 mg of Synacthen depot i.m. Take further blood samples at 0, 6 and 24 hours for cortisol estimation. Normal response is a peak at 4–6 hrs (about 900 nmol/L) and little further rise at 24 hrs. In Addison's disease there is no rise, in secondary adrenocortical failure little rise at 4–6 hrs with increased level at 24 hrs. An alternative is to give depot Synacthen 1 mg i.m. for 3 days and perform short Synacthen test on day 4.

B. Of the cause

1. Radiography – (a) Of abdomen – may reveal calcified adrenals of tuberculous disease. (b) Chest – may show tuberculous lesion or malignancy.
2. Adrenal auto-antibodies – are detected in about 55% of patients. In antibody negative patients, an autoimmune basis for the disease is suggested either by small adrenals on MRI (enlarged with tuberculous Addison's), or presence of other autoimmune diseases.

Differential Diagnosis

1. *Simmond's or Sheehan's disease* – Pigmentation of skin slight and patchy. No pigmentation of mucous membranes. Loss of pubic and axillary hair. Failure of sex function early and essential feature. Response to corticotrophic hormone of pituitary; this is absent in Addison's disease.
2. *Diseases associated with asthenia* – (i) Neurasthenia due to psychogenic factors. (ii) Hyperparathyroidism is often accompanied by extreme lassitude and weakness. Blood chemistry diagnostic. (iii) Myasthenia gravis – progressive weakness.
3. *Anorexia nervosa* – Usually in adolescent females, history of psychic trauma, marked anorexia, no pigmentation. Other psychic manifestations.
4. *Other causes of pigmentation* – (a) *Skin* – Pellagra, gastro intestinal tuberculosis, malabsorption, genetic, familial, malignant disease, liver disease, chronic kidney disease. (b) *Mouth* – pigmentation can be idiopathic or racial, and patchy pigment deposits in the lips are seen in syndrome of small intestinal polyposis. (c) *Other causes of local pigmentation* – include freckles, birthmarks and other pigmented naevi, melanomas, acanthosis nigricans, neurofibromatosis and polyostotic fibrous dysplasia. (d) *Pigments other than melanin* – Iron deposition in haemochromatosis, sliver deposits in argyria and haemosiderin in some bleeding diseases.
5. *Intestinal polyposis* – Spots of brown pigmentation may be present on the skin and lips as well as oral mucosa. Intestinal symptoms. Sigmoidoscopy or barium enema confirms diagnosis.
6. *Salt-losing nephritis* – Steroid output in urine normal but of aldosterone high. In Addison's disease both values low.

Management

Chronic hypoadrenalism

Replacement therapy:

(a) Cortisone (glucocorticoid) substitution – Initial: Hydrocortisone 20 mg (equivalent to 5 mg prednisolone or 0.5 mg delta or betamethasone) thrice daily for 72 hours. Maintenance – 20 mg morning and 10 mg evening. Dose best monitored by measuring series of serum cortisol levels throughout the day. The aim is to mimic the normal circadian rhythm of cortisol levels, with a peak of upto 650 nmol/L after the first dose of the day and an early morning nadir of < 200 nmol/L. Patients should be advised to double the dose and seek medical advice if they feel ill, e.g. respiratory infection with systemic upset, or if they undergo significant stress. Pregnancy may require an increase in hydrocortisone dose by 50% during the last trimester.

(b) *Aldosterone (mineralocorticoid) substitution* – Fludrocortisone 50–200 mg/day.

(c) *Salt* – Patients with curtailed food intake, diarrhoea or profuse sweating should be given an additional 3–6 gms of sodium chloride daily.

(d) *Adrenal androgen*- replacement is an option in patients with lack of energy, despite optimized glucocorticoid and mineralocorticoid replacement. It may also be indicated in women with features of androgen deficiency, including loss of libido. Adrenal androgen replacement can be achieved by once-daily administration of 25–50 mg DHEA.

Table 45: Cause of Cushing's syndrome

ACTH excess –
• Cushing's disease*
Ectopic ACTH secretion
• Carcinoma of lung (especially small cell)
• Carcinoid tumors of thymus or lung
• Medullary carcinoma of thyroid
• Carcinoma of colon
• Pheochromocytoma
Non-ACTH dependent
• Primary unilateral adrenocortical tumors (adenoma or carcinoma)
• McCune-Albright syndrome: Bilateral tumor (Gsα mutation)
• Primary pigmented nodular dysplasia
• ACTH – independent macronodular adrenal hyperplasia
Spontaneous Cushing's syndrome (rare)

*Cushing's disease is the most common cause of spontaneous Cushing's syndrome, occurring in 60-70% of pts. It results from ACTH hypersecretion by a pituitary corticotrophic adenoma.

Emergency management of Addisonian crisis: (a) Fluid resuscitation with normal saline. (b) Hydrocortisone – 100 mg i.v. bolus every 6 hours. Once patient is well enough, hydrocortisone 20 mg t.d.s. orally. This can be stepped down to maintenance over next 2 weeks.

ADRENAL CORTICAL HYPERFUNCTION

CUSHING'S SYNDROME

Cushing's syndrome refers to the clinical manifestations induced by, chronic exposure to excess corticosteroid. See Table 45 for the cause of Cushing's syndrome.

Cushing disease is corticosteroid excess due to pituitary dependent bilateral adrenal hyperplasia. The microadenomas, because of their size do not cause symptoms by local mass effect.

Clinical Features

Clinical features of Cushing's syndrome are listed in Table 46.

Table 46: Clinical features of Cushing's syndrome

Centripetal fat deposition
• Moon face
• Buffalo hump
• Truncal obesity
Protein-wasting effect of excess cortisol
• Striae: Commonly located on abdomen and flanks, purplish-red in colour and more than 1 cm in diameter
• Easy bruising, and slow healing of minor wounds
• Lower limb oedema
• Muscle wasting in upper arms and thighs, with fatiguability
• Osteoporosis particularly of vertebral bodies leading to compression fractures, back pain and loss of height
• Impaired defense against infection, often leading to superficial mucocutaneous infections.
Others
• Hypertension
• Hirsutism in men
• Psychiatric disturbance (e.g. anxiety, increased emotional lability, irritability). Psychosis may occur
• Retarded growth concomitant with weight gain
Electrolyte changes
• Hypokalaemia
• Glucose intolerance
• Mineralocorticoid oversecretion and genetic susceptibility

D.D. – 1. *Simple obesity* – No characteristic fat distribution, thin skin or proximal myopathy as in Cushing's 2. *Polycystic ovary syndrome* – associated with obesity and hirsutism. No other features of cortisol excess, and skin is thick. 3. *Chronic alcoholism* – History and other features of liver disease. High blood ethanol and γ-glutamyl transpeptidase (γ-GT) levels. Macrocytosis.

Diagnosis of Spontaneous Cushing's Syndrome

I. Tests indicating cortisol overproduction

1. *24-hour urinary cortisol excretion* – Increased value (>90 μg/day, 280 mmol/day) is diagnostic of hypercortisolism.
2. *Overnight dexamethasone suppression test*
   - Dexamethasone 1 mg p.o. between 11 pm and midnight; plasma cortisol measured next morning.
   - Normal individuals almost totally suppress cortisol production (plasma cortisol < 20 ng/mL, 50 nmol/L)
   - Used for positive diagnosis of Cushing's syndrome
3. *Low-dose dexamethasone suppression test*
   - Dexamethasone 2 mg/day p.o. for 2 days in 8 divided doses
   - Normal individuals almost totally suppress cortisol production (24-hour urinary cortisol excretion <10 μg, 50 nmol/L)
   - Used for possible diagnosis of Cushing's syndrome
4. *High-dose dexamethasone suppression test*
   - Dexamethasone 8mg/day for 2 days in 8 divided doses
   - Patients with Cushing's disease exhibit partial suppression of cortisol production (significant decrease in 24-hour urinary17-hydroxy steroids or cortisol excretion, usually >50%)
   - Patients with other causes of Cushing's syndrome (ectopic ACTH secretion syndrome, adrenal tumors) typically show significant variation in cortisol production
5. *Corticotrophin-releasing hormone test*
   - Synthetic bovine (or less often, human) corticotrophin releasing hormone 100 μg or 1 μg/kg i.v., plasma ACTH and cortisol measured during the next one hour
   - Patients with Cushing's disease are typically responsive (ACTH and/or cortisol plasma levels increase by >50% and/or 20%)
   - Patients with the ectopic ACTH syndrome or adrenal tumor are typically unresponsive.

II. For establishing the cause of cortisol overproduction

Assessment of Corticotrophin Function

Adrenal tumors – The presence of circulating ACTH coincident with hypercortisolism almost excludes a primary autonomous adrenocortical tumor. Adenomas typically secrete exclusively cortisol, whereas carcinomas secrete precursors and androgens.

Pituitary Disease or Ectopic ACTH

1. *Plasma cortisol and ACTH* – are both markedly elevated in ectopic ACTH secretion due to malignant tumors. A mean plasma ACTH above 400 ng/liter is unlikely to be due to pituitary disease.
2. *High dose dexamethasone suppressiontest* – In Cushing's disease there is fall in serum cortisol to less than 50% of the basal value.
3. *CRH test* – A pituitary adenoma (i.e. Cushing's disease) responds to pharmacological manipulation using CRH and there is partial suppression by high dose dexamethasone suppression test.

Imaging Techniques

Locate the tumor responsible for spontaneous Cushing's syndrome

1. *Pituitary MRI* – detects a microadenoma in up to 60%.
2. *Chest radiograph* – In ectopic ACTH syndrome, most tumors are located in the thorax: highly aggressive oat-cell carcinomas, or indolent bronchial carcinoids.
3. *CT scan* – Adrenocortical tumors are easily viewed.
4. *Octreoscan* – Scintigraphy with labelled somatostatin analogues is sensitive detecting tool for bronchial carcinoids.

Bilateral Inferior Petrosal Sinus Sampling

Allows collection of blood draining immediately from pituitary gland. In difficult cases, it establishes whether ACTH oversecretion is of pituitary or non-pituitary origin. In patients with Cushing's disease and negative pituitary MRI, it may help to localize the microadenoma before surgery. An increased central/peripheral plasma ACTH ratio >2 at baseline and >3 at 2–5 min after CRH injection is indicative of Cushing's disease.

Management

Cushing's disease – Transsphenoidal pituitary surgery (microadenomectomy). If surgery fails hypercortisolism can be controlled with antiadrenocortical drugs Metyrapone and Ketoconazole. If intolerance to these drugs, then Op'DDD which has specific adrenolytic action. Simultaneous radiotherapy is often indicated, allowing the anti-adrenocortical therapy to be discontinued later. In rare cases bilateral adrenalectomy may be necessary.

Ectopic ACTH syndrome – Surgical resection of tumor cures hypercortisolism in patients with more indolent tumors such as bronchial carcinoid. Chemotherapy may reduce ACTH secretion by oat-cell carcinoma of the lung.

ADRENOGENITAL SYNDROME

Clinical features – of excess of adrenal androgens may vary from slight hirsutism in the adult female to adrenocortical virilism. The manifestations depend on the age and sex of the individual – (a) *New-born infants* – When the fetus is exposed to excessive androgens there is pseudoprecocious puberty in the male and pseudohermaphroditism in the female. (b) *Children of either sex* – Precocious puberty of the male type, including muscular development and accelerated epiphyseal maturation. (c) *Adult female* – Virilization with enlargement of clitoris, premature axillary and pubic hair, muscular development and accelerated epiphyseal maturation. Because of inhibitory action of androgen on pituitary, breast development and menses do not occur.

PRIMARY ALDOSTERONISM (CONN'S SYNDROME)

Primary aldosteronism is the most common cause of mineralocorticoid hypertension (Table 47).

- Most cases are secondary to a solitary, small (0.5–2 cm) aldosterone-producing adenoma of adrenal gland. Female to male ratio is 3:1
- One-third cases are caused by bilateral adrenal hyperplasia
- Rarely, glucocorticoid-suppressible hyper-aldosteronism (GSH) is the cause.

Clinical Features

Presentation is usually with hypertension and hypokalaemia. Rare nonspecific symptoms include muscle weakness, nocturia and tetany. Severe hypertension may be associated with kidney and retinal disease.

Table 47: Causes of hyperaldosteronism

Primary aldosteronism
Syndrome of apparent mineralocorticoid excess (SAME)
Cushing syndrome
Glucocorticoid resistance
Adrenocortical carcinoma
Congenital adrenal hyperplasia
Progesterone-induced hypertension
Liddle's syndrome

Diagnosis

- Hypokalaemia – Spontaneous hypokalaemia (< 3.5 nmol/L) is uncommon in untreated hypertension. When found in a patient taking diuretics, these should be withdrawn, potassium stores replenished, and serum potassium remeasured after 2 weeks.
- Elevated plasma aldosterone levels
- Suppressed plasma renin activity

  The accepted screening test is concurrent measurement of plasma renin and aldosterone with subsequent calculation of the aldosterone-renin ratio (ARR); serum potassium needs to be normalized prior to testing.

  ARR screening is positive if the ratio is >750 pmol/L per ng/mL per hour, with a concurrently high normal or increased aldosterone. If one relies on the ARR only, the likelihood of a false positive ARR becomes greater when renin levels are very low.

  Saline infusion test - which involves the IV administration of 2 L of physiologic saline over a 4-h period. Failure of aldosterone to suppress below 140 pmol/L (5 ng/dL) is indicative of autonomous mineralocorticoid excess
- Abdominal CT or MRI to differentiate if possible hyperplasia from adenoma

Secondary hyperaldosteronism results from excess renin causing angiotensin stimulation of zona glomeruloza.

Causes – Accelerated hypertension, renal artery stenosis. Conditions associated with normal BP include heart failure and cirrhosis, where sodium retention results from excess aldosterone production.

DD of Adrenal Adenoma, Hyperplasia and GSH

1. *Effect of posture on aldosterone level* – In adrenal hyperplasia, erect posture increases plasma aldosterone.
2. *Administration of ACTH* – No effect on plasma aldosterone in adrenal hyperplasia, and small effect in adenoma, but marked rise in patients with GSH.

3. *Measurement of intermediary glucocorticoid metabolites* (e.g. 18-hydroxy cortisol or 18-oxocortisol/corticosterone) in plasma or urine. Levels are lowest in hyperplasia, higher in adenoma and much higher in GSH.
4. *Imaging* – Adrenal CT or MRI when biochemical tests have confirmed the diagnosis.

Differential Diagnosis – of Hypertension and Hypokalaemia

1. *Essential hypertension with* – (a) Vomiting and diarrhoea. (b) Diuretic therapy. (c) Oral contraceptives or oestrogen therapy. (d) Steroid therapy.
2. *Kidney disease* – (a) Accelerated or malignant hypertension. (b) Renovascular hypertension. (c) Potassium-losing nephropathies, e.g. chronic pyelonephritis. (d) Renin-secreting renal tumour.
3. *Adrenocortical dysfunction* – (a) Primary aldosteronism. (b) Cushing's syndrome and ectopic ACTH syndrome. (c) Endogenous mineralocorticoid excess (some adrenocortical tumours). (d) Exogenous administration of mineralocorticoid.
4. *Pseudo-aldosteronism* – (excessive liquorice ingestion).

Treatment – (a) *Adenoma* – should be removed. Spironolactone 300–400 mg/day for 3–4 weeks should be given as preparation for surgery. (b) *Bilateral hyperplasia* – Adrenalectomy contraindicated. Spironolactone 50–400 mg/day, or if not tolerated Amiloride 10–40 mg/day. Dexamethasone if GSH.

HYPERADRENALISM PHEOCHROMOCYTOMA

Pheochromocytoma is a catecholamine secreting tumour that arises from the chromaffin cells of the sympathoadrenal system. Ninety percent of all cases arise from the adrenal medulla. Extra-adrenal pheochromocytoma (paraganglioma) is usually encountered intra-abdominally. Ninety percent arise in the wall of urinary bladder. Intrathoracic origin is rare and is located in relation to paravertebral sympathetic chains.

Known associations – Neurofibromatosis, medullary carcinoma of thyroid and with hyperthyroidism (multiple endocrine adenomatosis).

Clinical Features

Hypertension – cardinal feature

(a) Paroxysmal – Attacks of paroxysmal hypertension arise suddenly lasting for minutes or hours. Usually brought on by emotional strain, or palpation of abdomen, or sudden change in posture such as lying on one or other side in bed at night. Symptoms are often paroxysmal
- Headache
- Sweating
- Palpitations
- Pallor (Patients with pheochromocytoma do not flush)
- Nausea
- Tremor
- Weakness
- Anxiety
- Epigastric pain
- Chest pain and dyspnoea
- Constipation

(b) Sustained hypertension – Some tumours secrete adrenaline and/or nor-adrenaline constantly causing persistent hypertension. Suspicion is aroused if signs of hyperthyroidism, intermittent glycosuria or frank diabetes.

Diagnosis

1. Biochemical test – Increased excretion of free catecholamines or their metabolites in urine – Vanilmandelic acid (VMA), normal 25 μmol (7 mg)/24 hr or metanephrines, normal 5.5 μ mol (1.0 mg)/24 hr, or total catecholamines normal 0.36 μ mol/24 hr (60 μg/24 hr).
2. Localization – Tumors are localized by CT or MRI scanning of abdomen or scintigraphy with ^{131}I-meta-iodobenzyl-guanidine (MIBG). If a tumour is not found in the adrenals, CT scan can be extended to include the rest of the abdomen, pelvis, chest and neck.

Management

Surgical removal of tumour. Pre-operative therapy to minimize risk of precipitous hypertension during surgery: α-blockade (phenoxybenzamine 20 mg t.d.s., increased to 240 mg/day if required) and β-blockade (propranolol 40 mg t.d.s., increasing to 240 mg/day if required) for minimum of 2–3 weeks before surgery.

7. PANCREAS

DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. Table 48 shows

Table 48: Etiologic classification of diabetes mellitus and impaired glucose tolerance

I. Type I DM (β-cell destruction, absolute insulin deficiency). Insulin dependent diabetes mellitus (IDDM)	
(a) Autoimmune	
(b) Idiopathic	
II. Type II DM – Non-insulin dependent (NIDDM)	
III. Maturity onset diabetes in young (MODY 1-6) Genetic defects in β-cell function have the following mutations:	
a. MODY 1 - Hepatocyte Nuclear Transcription factor (HNF) 4α	
b. MODY 2 - Glucokinase	
c. MODY 3 - HNF - 1α	
d. MODY 4 - Insulin promotor factor-1 (IPF1)	
e. MODY 5 - INF - 1β	
f. MODY 6 - Neurogenic differentiation1, (Neuro D1)	
IV. Secondary causes	
1. Pancreatic disease	
Cystic fibrosis	
Trauma/pancreatopathy	
Hemochromatosis	
Pancreatitis	
Fibrocalcific pancreatic diabetes (FCPD)	
Carcinoma of pancreas	
2. Endocrine disorders	
Acromegaly	Conn's syn.
Cushing's syn.	Pheochromocytoma
Glucagonoma	Hyperthyroidism
3. Drug-induced	
Glucocorticoids	Phenytoin
Diazoxide	Pentamidine
Thiazides	α-interferon
β-adrenergic agonists	Thyroid hormone
4. Infections	
Congenital rubella	Coxsackie B virus
Cytomegalovirus	
5. Insulin receptor defects	
Anti-insulin receptor antibodies (Stiffman syn.)	
Lipoatrophic diabetes	
6. Other genetic syndromes (sometimes associated with DM)	
Down's syndrome	
Turner's syndrome	
Wolfram's syndrome	
Prader-Willi syndrome	
Klinefelter's syndrome	
Laurence-Moon-Biedl syndrome	
Myotonic dystrophy	
Friedreich's ataxia	
Huntington's chorea	
Porphyria	
V. Gestational diabetes	
VI. Impaired glucose tolerance (Borderline diabetes)	
a. Primary: Obese, non-obese	
b. Secondary: All conditions mentioned under secondary DM, cirrhosis of liver, kidney failure, chronic undernutrition, hypokalaemia, stress, e.g. myocardial infarction.	

etiologic classification of diabetes mellitus and impaired glucose tolerance.

Pathogenesis

Type 1 diabetes – Due to a combination of genetic, autoimmune and environmental factors, there is destruction of pancreatic β cells.

1. **Genetic factors** – (a) Twin studies: Among monozygotic twins, the concordance rate is 30–70%, i.e. if one twin gets DM, the chances of second twin getting are 30–70%. (b) Major Histocompatibility Complex (MHC). Genes on the short arm of chromosome 6 encodes for Human Leucocyte Antigens (HLA). There is a strong association with Type I DM and HLA-DRD and HLA-DR4.
2. **Autoimmunity** Humoral and cell mediated immunity leads to lymphocytic infiltration of the islets of Langerhans called insulinitis. β cells are more susceptible to destruction by cytokines like TNF-α, TNF-γ, IL-1.

   Autoimmune basis is also suggested by association with other autoimmune diseases like Graves' disease, Coeliac disease, pernicious anaemia. Addison's disease, polyglandular autoimmune syndrome I and II.
3. **Environmental factors**
   (a) *Viruses:* Congenital rubella, mumps, coxsackie B, rotavirus.
   (b) *Chemical:* Nitrosourea compounds, Rodenticide, Pentamidine are associated with increased risk.
   (c) *Diet:* (i) Cow's milk (bovine milk proteins) may stimulate immune response against β cells. (ii) Wheat proteins (gluten). Gluten-sensitive enteropathy (coeliac disease) in 5–10% cases.
   (d) *Stress* in early life

Type 2 Diabetes (NIDDM)

Aetiopathogenesis

Type 2 DM is disorder characterized by insulin resistance and impaired insulin secretion. Hyperglycaemia develops due to (i) Peripheral resistance to action of insulin. (ii) Increased hepatic glucose output. (iii) Impaired pancreatic β cell secretion of insulin.

1. *Genetic factors:* Type 2 DM has very strong genetic predisposition.
   (a) Twin studies - Concordance in monozygotic twins is 70–90%. If both parents are diabetic, their off spring has 90% chance of developing type 2 DM.
   (b) Polygenic factors - Type 2 DM is a polygenic multifactorial disease, in majority of cases. No consistent major genetic genes has yet been implicated.
   (c) Monogenic forms are rare, e.g. Wolfram syndrome, MODY types 1-6, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke).
2. *Obesity lipotoxicity, nutrition.*
   (a) Obesity and central fat distribution. The cut offs for BMI are 23 kg/m^2 and waist circumference for men at 90 cm and for women 80 cm.
   (b) Lipotoxicity. Adipose tissue can secrete a large number of 'adipokines' which can impair insulin secretion and action by an endocrine effect, e.g. leptin or increase in insulin resistance, e.g. TNF-α, Resistin, Adinopectin (low levels contribute to insulin resistance). Free fatty acids inhibit glucose uptake and increase hepatic glucose output.
3. *Environmental factors*
   (a) Nutrition: Generous dietary intake
   (b) Physical inactivity
   (c) Vitamins and trace elements - Low levels of Vitamin D, zinc, copper, chromium.
4. *Insulin resistance.* It is a state in which a given concentration of insulin gives a subnormal biological response on patients target tissue e.g. skeletal muscle, adipose tissue and liver. There is resistance to exogenous and endogenous insulin. There are overt diabetics who do not respond to conventional and supraphysiological levels of insulin, but at the end are commonly seen in individuals with mild glucose intolerance. It is also called metabolic syndrome. Deadly quartet-CHAOS (CAD, HT, Obesity, Adult onset diabetes and Stroke). See Table 49 for the criteria of insulin resistance.
5. *The 'thrifty phenotype' hypothesis* – Individuals with low birth weight appear to have higher risk of NIDDM, particularly if they become obese in later life. This hypothesis suggests that intra uterine malnutrition leads to defective pancreatic development. Such individuals may become susceptible to diabetes, hypertension and heart disease in later life.

Table 50 gives distinguishing features between IDDM and NIDDM.

Table 51 enlists risk factors for type 2 diabetes.

Table 49: Criteria for diagnosis of IR (WHO).

• Central obesity (BML, WHR)
• Low Tg (>150 mg/L, high LDL)
• Low HDL (< 40-50 mg/dL)
• High BP (>130/85 mm Hg)
• FBS >100 mg/dL

Table 50: Distinguishing features between IDDM and NIDDM

	IDDM (Type 1 DM)	*NIDDM (Type 2 DM)*
Body habitus	Normal or thin	Obese
Acute complication	Ketoacidosis	Hyperosmolar coma
Plasma insulin	Low to absent	Normal to high
Auto-antibodies	Present	Absent
Sulphonyl therapy	Unresponsive	Responsive
Insulin therapy	Responsive	Responsive to resistant
Family h/o diabetes	No	Yes
Age at onset	<40	>40

Endothelial Dysfunction in Diabetes

Atherosclerosis is the leading cause of death in diabetic patients. It is an early abnormality and may play a key role in the micro and macrovascular disease condition associated with the disease. Several measures have been shown to cause improvement in endothelial dysfunction including exercise and wt. loss, lipid lowering, ACE inhibitors, antioxidants, reducing homocysteine levels, reducing

Table 51: Risk factors for type 2 diabetes

• Age ± 45 years
• Overweight (BMI ≥ 25 kg/m^2)
• Family history of diabetes (parents or siblings with diabetes)
• Habitual physical inactivity
• Previously identified IFG or IGT
• History of GDM or deliver of a baby >9 lbs
• Hypertension (≥ 140/90 mm Hg in adults)
• HDL cholesterol ≥35 mg/dL (0.9 mmol/L) and/or triglyceride level ≥250 mg/dL (2.82 mmol/L)
• Polycystic ovary syndrome
• History of vascular disease

hyperglycaemia and nitric oxide co-factors like tetrahydrobiopterin and modulation of insulin resistance.

Latent diabetics – are those with normal glucose tolerance test who have had abnormal tests in certain forms of beta-cell stress, e.g. during pregnancy or infection, when obese, or during treatment with drugs such as corticosteroids.

Clinical Features

Onset – Usually gradual in adults, but acute in children.
Modes of presentation –

- Presence of osmotic symptoms (polyuria, polyphagia, polydipsia)
- Weight loss, fatigue and lassitude
- Pruritus vulvae in females or balanitis in males
- Loss of libido or erectile dysfunction
- Blurring of vision
- Accidental discovery or asymptomatic glycosuria (e.g. during life insurance examination)
- Symptoms due to diabetes - related complications e.g. abdominal pain in ketoacidosis (Table 52)

Convulsions – Fits should be considered hypoglycaemic until proved otherwise, especially in children. EEG abnormalities are common in insulin-treated patients, especially those with recurrent hypoglycaemia. Day time attacks suggest epilepsy, while nocturnal attacks are often hypoglycaemic.

Laboratory Investigations in Diabetes

1. **Blood glucose estimation**

   In non-diabetes, blood glucose levels are 70-100 mg/dl.

Table 52: Abdominal pain in diabetes:

1. Gastric dilatation (a) Acute – Ketoacidosis. (b) Chronic – Autonomic neuropathy.
2. Pancreatitis (a) Acute following development of type IV hyperlipidaemia. (b) Chronic – precedes development of diabetes.
3. Infarction (a) Mesenteric. (b) Myocardial (Painless in autonomic neuropathy).
4. Genitourinary (a) UTI. (b) Bladder retention.
5. Hepatobiliary (a) Cholecystitis. (b) Fatty infiltration of liver causing hepatic capsular distension. (c) Thoracolumbar radiculopathy.

   (a) *Random blood glucose* is done at any time in the day, irrespective of meals. If <140 mg normal, >200 mg indicates DM and between 140–200 mg, GTT is required.

   (b) *Fasting blood glucose* is measured after 12 hr fast. Normal <100 mg, diabetes if >126 mg and impaired fasting glucose 101–125 mg (pre-diabetics).

   (c) *Post-prandial blood glucose* is measured 2 hr after a meal. Normal <140 mg, Diabetes >200 mg Impaired glucose tolerance 140–199 mg.

2. **Oral glucose tolerance test (OGTT)**

   Pre-diabetes also known as impaired glucose tolerance is a condition with no symptoms but these pts. can develop more serious type DM. Hence individuals with family history of DM type 2, women who had gestational diabetes or had a baby weighing > 9 pounds, the obese with much belly fat and the elderly should undergo the test. In OGTT the first sample is taken after an overnight fast of 8 hrs following which patient is given glucose 1 g/kg body wt. Blood is then collected at 30, 60, 120 and 180 minutes. In diminished glucose tolerance, level of blood glucose is highly raised at 180 minutes.

   Factor affecting GTT

   1. Age – GTT decreases in patient > 60 years of age
   2. Obesity
   3. Surgery – Due to stress of surgery, there is increase in cortisol and catecholamine secretion.
   4. Drugs – Thiazides, phenytoin, oral contraceptives, thyroxine, corticosteroids.

   Urine glucose – Normally about 100 mg/d is excreted and can be estimated by tests for reducing sugar e.g. Benedict's tests or clinistix method. Those measurements are now not recommended.

3. **Glycosylated haemoglobin (GHb)**

   It is used to measure long-term glycaemic control. Hb in the blood is glycated by glucose. Glucose combines with protein residues on Hb chains by slow 'Non-enzymatic glycation'. This results in formation of Hemoglobin A1c proportionate to amount of blood glucose (Table 53**)**. Since life span of RBCs is 21 days, the HbA1c will reflect blood glucose levels over last 2–3 months. Table 54 gives clinical value of glycohaemoglobin assays.

   Advantages - No relation to meals, physical activity, crash diets or modes of therapy.

   Disadvantages - (a) Cannot be used to change daily diseases of drugs or insulin. (b) Values are unreliable in hemolytic anaemias and haemoglobinopathies because of reduced life span of RBCs. (c) In iron deficiency anaemia,

Table 53: Correlation between HbA1c and mean blood glucose levels

HbA1c	*Mean blood glucose (mg/dL)*
5	100
6	135
7	170
8	205
9	240
10	275
11	310
12	345

values are higher, lower values in pregnancy, Vitamin C, E deficiency.

Self-monitoring of Blood Glucose

- Type I diabetes 4–6 times a day depending on the insulin regimens.
- Type II diabetics on oral hypoglycaemic drugs need to monitor 1-2 times/d.
- During pregnancy more frequent monitoring.
- During acute complications or illness 2-hourly.

3. **Microalbumin.** Pts with microalbuminuria have a greater risk of developing kidney failure, and cardiovascular damage. Reference is 0-1.7 mg/dl in spot random sample, upto 20 mg/L in 24 hr urine volume.
4. **Urine protein/creatinine ratio** gives information about proteinuria in pts with diabetic nephropathy. Higher the ratio, greater the damage.
5. **Serum creatinine.**In diabetics with nephropathy a doubling of creatinine suggests a 50% reduction in GFR.
6. **Insulin levels.**Elevated blood glucose levels with low insulin levels indicate insufficient insulin for adequate control of blood glucose. Similarly high insulin levels with low blood glucose indicate a change in dosage of drugs.
7. **C-peptide** is used to monitor beta cell activity and capability over time and help in deciding when to start insulin therapy. C-peptide in conjunction with insulin and glucose levels can be used to diagnose cause of hypoglycaemia and monitor its treatment.
8. **Insulin antibody test**– Quantitative determination of antibodies against insulin in serum.
9. **GAD-65 antibody** is an enzyme produced primarily by pancreatic islet cells. GAD-65 antibodies are common in newly diagnosed diabetic patients and often appear years before clinical onset of the disease.

Table 54: Clinical value of glycohaemoglobin assays

- Estimates average blood glucose level over previous 2–3 months
- Identifies patients that may require intensification of treatment
- Assesses impact of treatment changes during previous 1–2 months
- Predicts pregnancy outcome and foetal macrosomia
- Predicts risk of long-term complications over 3–10 years
- Allows comparison of glucose control among different populations
- Unaffected by short-term (hours) changes in glucose concentration
- Self-monitoring of blood glucose by patients at home

Table 55: Markers of IDDM

1. Genetic markers
2. Islet cell antibodies (ICA)
3. Insulin autoantibodies (IAA)
4. Elevated proinsulin levels
5. Circulating adhesion molecules
6. Antiglutamic acid decarboxylase (64K anti-GAD).

Presence of the antibody – (a) Is a strong predictive marker for onset of type 1 DM. (b) Helps differentiate between Type 1 and Type 2 diabetes. (c) Aids in prediction, diagnosis and management of DM. (d) Indicates need for progression to insulin therapy in Type 2 DM. (e) To determine the cause of hypoglycaemia. (f) To monitor recovery after removal of an insulin-producing tumor of the pancreas.

Early detection of IDDM – Some of the markers that can predict the development are given in Table 55.

PREGNANCY AND DIABETES

Pregnancy predisposes to diabetes by three mechanisms.

1. Antagonization of peripheral actions of insulin due to raised levels of oestrogens, progesterone, corticosteroids, human chorionic somatomammotropin and human placental lactogen.
2. Rapid insulin destruction due to high insulinase activity of placenta.
3. Depletion of β cell insulin reserve. Increased utilization of stored nutrients and glucose to feed the foetus leads to fasting hypoglycaemia, ketonaemia and elevated free acids which leads to insulin release and ultimately depletion of beta cell insulin reserve.

See Table 56 for the adverse effects of diabetes on pregnancy and Tables 57 and 58 for effects on foetus.

Management of diabetes in pregnancy

1. Diet high protein intake. Restriction of salt if oedema.
2. Exercise.
3. Insulin therapy is essential. In first half of pregnancy requirement may be reduced due to morning sickness. Constant glucose utilization through the placenta and absence of antagonists to maternal glucose utilization. Post-partum insulin dosage must be readjusted as insulin requirements fall due to removal of placental lactogen.
4. Oral hypoglycaemic agents should be avoided except metformin which is effective in women with PCOD to aid conception.

Table 56: Adverse effects of diabetes on pregnancy

• Polyhydramnios
• Pre-eclampsia, eclampsia
• Recurrent abortions
• Premature labour
• Prolonged labour
• Abnormal presentations
• UTI
• Monilial vaginitis
• Hypoglycaemia (first trimester)
• Hyperglycaemia (third trimester)
• Postpartum hemorrhage
• Puerperal sepsis
• Retinopathy
• Nephropathy
• Gastropathy
Adverse effect on foetus
• Macrosomia (large babies) because of foetus/hyperinsulinaemia causing excessive fat deposition and visceromegaly.
• Prematurity.
• Post-partum hypoglycaemia from persisting insulin secretion after birth in absence of glucose supplied via placenta.
• Intra-uterine death more common after 37th week, hence early termination of pregnancy is advisable especially if she has vascular complications.

Foetal monitoring in GDM for foetal anomalies

(a) USG at 18–22 wks for malformations.

(b) Foetal echo at 20–24 wks.

(c) Serum α-fetoproteins.

(d) Chromosomal studies if required.

For foetal well-being

(a) Maternal records of foetal movements. (b) Foetal heart rate patterns (cardiotomography). (c) USG. Non-stress test, contraction. (d) Lecithin: Sphingomyelin ratio (for lungs).

Renal glycosuria is a rare condition in which sugar is eliminated in urine despite a normal or low blood sugar. This is due to improper functioning of renal tubules. When glucose in blood increases beyond 180 mg/dL, it is excreted in urine. This point is known as renal threshold for glucose (RTG).

SPECIAL CATEGORIES OF DM

1. Late-onset Autoimmune Diabetes of Adults (LADA) – A variation of type 2 DM, patients have autoantibodies such as anti-islet cell and anti-glutamic acid (GAD)

Table 57: Effects of diabetes on fetus

First trimester	*Second trimester*	*Third trimester*
Foetal malformation Growth retardation Foetal loss Placental Macrosomia insufficiency	Hypertrophic cardiomyopathy Resp. distress Foetal loss Low IQ	Hypoglycaemia Hypocalcaemia Hypomagnesaemia Polycythaemia Intra-uterine death

Table 58: Malformations due to diabetes in fetus

Cardiac	*Neurological*	*Renal*	*Skeletal*	*GI tract*	*Endocrine*
VSD Conus arteriosus Dextrocardia	Sacral agenesis Caudal regression syn. Anencephaly Myelocoele Hydrocephalus	Renal agenesis Ureteric duplication	Sacral agenesis Cleft lip/cleft palate Arthrogryposis	Anorectal atresia	Pseudo- hermaphrodism

antibodies. Insulin levels are low. However, they progress gradually and present in non-obese young adults and may respond to OHAs. Eventually they became insulin dependent.

2. Maturity onset Diabetes of the Young (MODY2) is inherited genetic defect in β-cell glucokinase function defect. Patients are detected during routine screening or during pregnancy. The hyperglycaemia is minimal. MODY 1,3,4,5,6 present in early adulthood, are symptomatic, have severe hyperglycaemia and are prone to develop complications.
3. Fibro Calculous Pancreatic Diabetes (FCPD). See later.
4. Brittle diabetes – Here patients have wide fluctuations in blood sugar and recurrent episodes of ketoacidosis in spite of adequate doses of insulin. It usually occurs in young females with psychiatric problems and menstrual irregularities.

Management of Diabetes Mellitus

See Table 59 for the goals in management of diabetes.

Diet

- Restoration of normal blood glucose and optimal lipid levels.
- Maintenance of blood glucose level as near to physiologic levels to prevent onset or progression of complications.
- Maintenance of normal growth rate in children and adolescents as well as attainment and maintenance of reasonable body weight in adolescents and adults.
- Provision of adequate nutrition for pregnant women, the fetus and during lactation.
- Consistency in timing of meals and snacks to prevent inordinate swings in blood glucose levels.
- Motivation to have small frequent meals.

Table 59: Goals in the management of diabetes

• Elimination of the catabolic state and its symptoms
• Elimination of glycosuria
• Achievement of preprandial and post-prandial euglycaemia as indicated by normal HbA_1C
• To prevent or retard the progression of complications associated with diabetes
• Prevent metabolic crises like ketoacidosis and hypoglycaemia
• Maintain normal growth and body weight
• Encourage self-reliance and self-care
• Ensure optimum quality of life

- Determination of a meal plan appropriate for individual's lifestyle and based on dietary history to have good compliance.
- Management of weight reduction for obese individuals with NIDDM.
- Improvement in the overall health of patients with diabetes through optimal nutrition.

Total calories –

Requirements are determined by the patient's activity (Table 60).

Overweight NIDDM should be encouraged to establish their weight within a desirable range. A reduction of approximately 500 kcal/day can result in loss of 1–2 kg/month.

Carbohydrates – should comprise 55–60% of the calories, with the form and amount to be determined by individual eating habits and blood glucose and lipid responses. Unrefined carbohydrates should be substituted by refined carbohydrates to the extent possible.

Proteins – Recommended dietary allowance of 0.85 g/kg body weight for adult is an appropriate guide. If kidney dysfunction, reduce intake to 0.6 g/kg.

Fat – should comprise ≤ 30% of total calories and all components should be reduced proportionately. Replacement of saturated with polyunsaturated fat is desirable to reduce cardiovascular risk. Cholesterol intake should be < 300 mg/day.

Fibre – Increased consumption of dietary fibre especially soluble fibre are associated with lower levels of blood glucose and serum lipids. The water insoluble fibres such as cellulose, lignin and most hemicelluloses found in whole grain breads, cereals and wheat bran affect gastrointestinal transit time and faecal bulk with little impact on plasma glucose. However highly viscous water soluble fibres such as pectins, gums and storage polysaccharide found in fruits, legumes, lentils roots, tubers, oat and oat bran, when eaten in purified form, reduce serum levels of glucose and insulin. Ideal recommended amount of fibre in patient's diet is 35–40 g/day.

Table 60: Caloric requirements

	Types of activity		
Nutritional status	*Sedentary*	*Light work*	*Heavy*
	Calories per kg body weight		
Obese	25	30	35
Normal	30	35	40
Lean	35	40	45

Alternative sweeteners – Both nutritive and non-nutritive sweeteners are acceptable in diabetes management.

Sodium – Should be restricted to 1000 mg/1000 kcal, not to exceed 3000 mg/d to minimize symptoms of hypertension.

Alcohol – in moderation and may need to be restricted entirely by person with diabetes and insulin-induced hypoglycaemia, neuropathy, poor control of glucose and lipids, or obesity.

Vitamins, minerals and antioxidants – intake should be encouraged.

(a) **Forbidden foods –** Sugar, jam, jellies, honey, jaggery, tinned fruits and juices, sweets, chocolate, ice creams, pastries, glucose drinks, foods made with sugar, pudding, sauces.

(b) **Foods allowed in moderation** – Bread of all kinds and chapattis made from wheat or millets, plain biscuits, all fresh fruits, baked beans, breakfast cereals.

(c) **Free foods –** All meat, fish, eggs (not fried), clear soup or meat extracts; tea or coffee; vegetables such as cabbage, cauliflower, spinach, pumpkin, brinjal, lady's finger, turnip, French beans, cucumber, lettuce, tomato, spring onions, radish, asparagus. Spices, salt, pepper and mustard; butter and margarine. Sugar substitutes for sweetening.

Exercise

See Table 61 for the potential risks and benefits of exercises.

Table 61: Risks and benefits of exercises

Potential benefits of exercises

- Maintenance of desirable body weight
- Improved sense of wellbeing and enhanced social interactions
- Enhanced insulin sensitivity
- Improved glucose control
- Decreases triglycerides and increases HDL-cholesterol levels
- Improved fibrinolysis
- Improved cardiac performance

Potential risks of exercises

- *Cardiovascular* – Myocardial ischaemia or infarction, dysrhythmias. Hypertensive response to exercise.
- *Microvascular* – Retinal haemorrhage, proteinuria, accelerated microvascular disease.
- *Metabolic* – Hypoglycaemia, hyperglycaemia, ketosis.
- *General* – Muscle strains/sprains, foot injury, joint injury, degenerative arthritis, poor dietary compliance.

Medical evaluation prior to formulating exercise programme

- History and physical examination
- Review of diet and medication
- Fundoscopy
- Foot evaluation

Neurological evaluation – (a) Sensory/motor. (b) Autonomic –

- Cardiovascular risk-factor profile
- Stress test assessment of glucose control

Exercise prescription

Type – Must be adjusted to patient's preference and existing medical condition. Aerobic exercise is preferred (swimming, cycling, walking, running). Addition of moderate resistance should be considered.

Duration – 20–45 mins. per session.

Frequency – 3–4 sessions per week is required to observe beneficial metabolic effects. 4–5 sessions per week for weight reduction.

ADA recommends 150 min/week (distributed over at least 3 days) of moderate aerobic physical activity with no gaps longer than 2 days.

Intensity – Patient's maximal pulse rate is estimated by subtracting patient's age from 220. Patient can be started at 40 to 50% of their maximal pulse rate with gradual increments to 60–70% over 6–8 weeks.

Programme

- Stretching (5–10 mins)
- Warm up (5–10 mins)
- Exercise (20–45 mins)
- Warm down (10 mins at 30% of full exercise intensity)

Exercise should be avoided when plasma glucose concentration is >250 to 300 mg/dL and/or presence of ketones in urine.

Oral Antidiabetic Drugs (OADs)

Insulin Secretagogues

Sulphonylureas **–** Lower blood glucose levels and are effective orally. See Table 62 for the characteristics of commonly used sulphonylureas Table 63 for response to sulphonylureas.

Mode of action – The sulphonylureas bind to a specific sulphonylurea receptor on pancreatic beta cells and exert their insulinotropic effects by closing adenosine triphosphate (ATP)-dependent potassium channels. This in turn, causes depolarization of the beta cells, which promotes influx of calcium and stimulation of insulin secretion.

Table 62: Characteristics of commonly used sulphonylureas

Drug	*Initial daily dose (mg)*	*Doses/day*	*Comments*
First generation			
Acetohexamide	250 mg	1–2	Has diuretic and uricosuric activity
Chlorpropamide	100 mg	1–2	Can potentiate ADH Disulfiram-like action with alcohol in 1/3rd of pts.
Tolazamide	100 mg	1–2	Has diuretic activity
Second generation			
Glibenclamide	2.5–20 mg	1–2	Hypoglycaemia can be severe
Gliclazide	40–320 mg	1–2	Metabolism/excretion by liver/kidney
Glipizide	5 mg	1–2	Mild diuretic activity
Glyburide	2.5 mg	1–2	Highest risk of hypoglycaemia
Glimepiride	1 mg	1	Excreted in urine and bile

Table 63: Diabetics likely to respond to sulphonylureas

- Onset of diabetes after 30 years of age
- Short duration of diabetes (5 years)
- Residual beta cell function
- Absence of GAD and islet cell antibodies
- Normal weight or moderately obese
- Fasting glucose <250 mg/dL

Table 64: Causes of secondary sulphonylurea failure

Natural history of NIDDM
- Progressive β cell failure: genetic
- Progressive insulin resistance: genetic

Patient-related
- Dietary non-compliance/weight gain
- Poor compliance with medication
- Lack of exercise
- Stress, intercurrent illness

Therapy-related factors
- Glucose-toxicity
- Inadequate doses
- Simultaneous use of diabetogenic drugs.

Sulphonylureas also probably exert extra-pancreatic effects on both the liver and peripheral muscle tissues.

First generation sulphonylureas have greater incidence of hypoglycaemia and more chances of drug interactions. Hence, second generation drugs are preferred. In patients with significant kidney disease is advisable to use Tolazamide, as it is exclusively metabolized by the liver.

Timing – Sulphonylureas should be taken 30 mins. prior to meals initially, because acute release of insulin results in lower postprandial plasma glucose excursion than when the drug is taken together with the meal. However, after several months, the acute insulin response wanes and the need to take the drug prior to meal becomes less evident.

In symptomatic patient with fasting blood sugar >250–300 mg/dL, or urinary ketones positive, therapy should be initiated with insulin.

Approximately, 20 to 25% of diabetics fail to respond to sulphonylureas. (primary failure). Those who respond initially to oral hypoglycaemic agents and then as the duration of diabetes increases glycaemic control deteriorates (secondary failure). The rate of secondary failure is about 4-5% per year (Table 64).

Table 65 gives contraindications and adverse effects and Table 66 drug interactions of sulphonylureas.

Insulin Sensitizers

Biguanides: ***Metformin*** – a guanidine derivative, effective and safe for control of hyperglycaemia (Table 67). Table 68 lists contraindications for the use of metformin.

Proposed mechanism of action

- Causes anorexia
- Decreases intestinal absorption of glucose
- Increases muscle and adipose tissue glucose uptake
- Decreases hepatic insulin resistance and thereby gluconeogenesis and glucose production.

Indications

NIDDM patients, obese or normal weight as monotherapy or in combination with sulphonylurea or insulin.

Dosage: 1.5 g to 2.5 g/day in 3 divided doses after meals

Side effects – Metallic taste, anorexia, nausea, abdominal discomfort and diarrhoea. These are mild, transient and self-limiting, subsiding after first 2 to 3 weeks

Table 65: Contraindications and adverse effects of sulphonylureas

Contraindications
- Type 1 diabetes mellitus
- Pancreatic diabetes
- Gestational diabetes
- Allergy to sulphonylureas
- Severe infection, stress, trauma
- Major surgery
- Kidney and liver dysfunction

Adverse effects of sulphonylureas
- Hypoglycaemia
- Allergic reactions
- Skin rash
- Haematological abnormalities
  - Haemolytic anaemia
  - Thrombocytopenia
  - Agranulocytosis
- Facial flushing – (antabuse effect of chlorpropamide)

Table 66: Sulphonylureas and drug interactions

Deterioration of glycaemic control
- Drugs that increase sulphonylurea metabolism (Rifampicin, barbiturates)
- Inhibitors of insulin secretion. (Thiazides and loop diuretics, β adrenergic blockers, phenytoin)
- Inhibitors of insulin action (steroids, growth hormone)

Increase in hypoglycaemia
- Drugs that displace sulphonylurea from albumin binding sites (Aspirin, fibrates, trimethoprim)
- Competitive inhibitors of sulphonylurea metabolism (H_2 blockers, alcohol)
- Inhibitors of renal excretion (probenecid, allopurinol)
- Antagonist of counter regulatory hormones (sympatholytic drugs, β adrenergic blockers)
- Concomitant use of drugs with hypoglycaemic action (Alcohol, aspirin)

Table 67: Beneficial effects of metformin
- Decreases blood glucose:
  - Decreases fasting glucose by 60-70 mg/dl
  - Decreases the increment in plasma glucose after meals
- Does not increase plasma insulin levels
- Induces weight loss
- Improves plasma lipid profile:
  - Decreases LDL cholesterol and triglycerides
  - Decreases postprandial hyperlipidaemia

Table 68: Contraindications of metformin
- Renal insufficiency (creatinine >1.5 mg/dl or GFR < 60 mL/min)
- Hepatic failure
- Severe cardiac disease
- Severe pulmonary disease with hypoxaemia
- Severe trauma, systemic infection or shock
- Pregnancy

of therapy. Small initial doses and administration with meals minimizes side effects. Lactic acidosis if contraindications are not observed before starting metformin.

Malabsorption of vitamin B_{12} in about 30% of patients

Underweight patients – or those whose control remains poor despite weight reduction are often markedly insulin deficient (severe lethargy, polyuria, persistently elevated HbA_1 values, rapid weight loss, ketonuria) should be treated with insulin. When there is uncertainty about residual insulin secretion, estimation of endogenous insulin secretion by glucagon stimulations test may be useful. Basal blood sampling for glucose and c-peptide is carried out after overnight fast. Glucagon 1 mg bolus is given i.v., blood sampling is done at 5 minutes for glucose and c-peptide.

Moderately obese patient – Full doses of metformin are started on combined therapy with a sulphonylurea, with gradual dose increments until blood sugar levels fall, or maximum doses of both the drugs are reached. Younger patients or older patients with symptomatic hyperglycaemia if poorly controlled, on combined therapy need insulin therapy.

Thiazolidinediones

Mode of action. Selective action for nuclear peroxisome proliferator activated receptor gamma (PPAR-r), followed by activation of insulin responsive genes that regulate carbohydrate and lipid metabolism. The drug primarily reduces insulin resistance in peripheral tissues and also longer glucose production by the liver.

Contraindications – (a) type 1 DM. (b) Liver dysfunction. (c) Class III or IV cardiac disease.

Dose: 15–48 mg bd can be combined with sulphonylurea metformin.

Side effects - (a) Peripheral oedema (b) precipitation of cardiac failure (c) worsening of diabetic macular oedema.

Alpha-glucosidase Inhibitors

Acarbose/Voglibose. Its major action is to lower postprandial plasma glucose levels, while causing a modest reduction in fasting plasma glucose concentration. See Table 69 for the indications and contraindications of alpha-glucosidase inhibitors.

Mode of action – Inhibition of breakdown of complex carbohydrates within the intestine, thus resulting in delayed absorption of glucose within small bowel and a consequent reduction in post-prandial glucose levels. Acarbose inhibits enzymes known as alpha-glucosidase. These enzymes cleave oligo- and disaccharides into monosaccharides, which then are rapidly absorbed from GI-tract. There are several intestinal alpha-glucosidase including glucoamylase, sucrase, maltase, isomaltase and lactase. The inhibitory effect on various alpha glucosidase are variable.

Dose – Acarbose 25–100 mg t.d.s. Voglibose 0.2–5 mg t.d.s. It is taken orally three main meals. In combination with metformin 500 mg for increased efficacy.

Side effects – Bloating, abdominal discomfort, diarrhoea and flatulence. These tend to diminish with continued use of the drug.

Insulin Secretagogues (Glinides, Meglitinides) (Repaglinide, Nateglinide)

Mechanism of action – closely resembles that of sulphonylurea. The meglitinides stimulate release of insulin from pancreatic β cells and there action is mediated through a different binding site on the sulphonylurea receptors of the β cells. They have a very short onset of action and short half-life (about 1 hour). They are useful in decreasing PPG and have a low risk of hypoglycaemia, especially Nateglinide. Elevation of liver enzymes has been reported with repaglinide.

Table 69: Indications and contraindications of alpha-glucosidase inhibitors

Indications

- Monotherapy in patients with mild to moderate hyperglycaemia.
- Adjunctive therapy in patients on sulphonylurea but who have suboptimal glycaemic control.

Contraindications

- Underlying disorder of GI-tract including inflammatory bowel disease, colonic ulceration.
- Pregnancy and lactation.
- Serum creatinine >2.5 mg/dL.
- Cirrhosis of liver.

Doses

Repaglinide – 0.5 mg three times a day to a maximum of 4 mg per dose and 16 mg/per day.

Nateglinide – 60-120 mg t.d.s to be taken 30 minutes prior to meals.

Combination therapy of two drugs is often required to achieve good blood glucose control. If glycaemic control cannot be achieved, insulin therapy is preferred to addition of a third drug.

DPP-4 Inhibitor (Vildagliptin, Saxagliptin)

Mode of action – inhibit degradation of native GLP-l and thus enhance the incretin effect. Improve islet cell function by increasing α and β cell responsiveness to glucose.

Dosage

Vildagliptin 50–100 mg daily in 2 divided doses with meals.
Saxagliptin 2.5-5 mg od

Reduced doses should be given to patients with renal insufficiency.

Human Glucagon-like Peptide-1 (GLP-1) Analogue Liraglutide, Exenatide

Mode of action – The drug supplements the body's own GLP-1 to trigger the secretion of insulin into the blood. It acts also stops the liver from releasing too much sugar into the blood. It acts when it is needed, when sugar levels are elevated after a meal.

Both the analogues are associated with reduced risk of hypoglycaemic episodes, including nocturnal hypoglycaemia to half the level seen with NPH.

The potential advantage of insulin detemir is low risk of hypoglycaemia when compared with insulin glargine. Also it has weight-sparing effect when compared with NPH insulin and insulin glargine.

Side effects – Nausea is the most common adverse effect leading to withdrawal.

Amylin Agonist

Patients who are insulin deficient are also amylin deficient, an analogue of amylin (pramlintide) was created and found to reduce postprandial glycemic excursions in

Table 70: Insulin preparations

Insulin preparation	*Onset (Hrs)*	*Peak (Hrs)*	*Duration (Hrs)*
Rapid acting			
Regular	½–1	2–4	6–8
Lispro (analogue)	¼–½	1–2	3–5
Intermediate acting			
NPH (isophane)	1–4	8–10	12–20
Lente (insulin zinc suspension)	2–4	8–12	12–20
Long acting Ultralente (extended insulin zinc suspension)	3–5	10–16	18–24

type 1 and type 2 diabetic patients taking insulin. Pramlintide slows gastric emptying and reduces glucagon secretion. It is used as subcutaneous injection.

Side effects are nausea and vomiting. Because pramlintide slows gastric emptying, it may influence absorption of other medications and should not be used in combination with other drugs that slow GI motility.

Sodium-Glucose Co-Transporter 2 Inhibitors (SLGT2)

Mode of action - Lower the blood glucose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal convoluted tubule in the kidney. This inhibits glucose reabsorption, lowers the renal threshold for glucose and leads to increased urinary glucose excretion. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion.

Side effect - Due to the increased urinary glucose, urinary or vaginal infections are more common and the diuretic effect can lead to reduced intravascular volume.

Example – Canagliflozin, dapagliflozin and empagliflozin

Insulin

Early intensive treatment of new onset DM aimed at high glucose control reduces the risk of microvascular complications and probably also macrovascular disease. "Metabolic memory" and legacy effect are terms that have been used to describe the fact that glucose control early in diabetes profoundly influences the prognosis later on in life. Most patients with Type 2 DM ultimately require insulin to attain glycaemic targets.

Types of insulin

Species of origin – Bovine, Porcine, recombinant DNA technology - Human.

Table 71: Indications of insulin

- Type 1 diabetes
- Gestational diabetes
- Hyperglycaemia despite maximum doses of oral agents
- Decompensation due to intercurrent events such as infection, acute injury or stress
- Development of severe hyperglycaemia with ketosis
- Perioperative in patients undergoing surgery
- Kidney or hepatic disease

See Table 70 for the insulin preparations and Table 71 for the indications.

Treatment Strategies

1. *Single dose regimen* – Daily injection of intermediate acting insulin given before breakfast. The starting dose 0.3 to 0.4 U/kg/day; increased gradually to obtain glucose values in acceptable range. Regular insulin can be added to decrease the glucose level that follows breakfast.
2. *Twice daily regimen* – Combination of regular and intermediate acting insulin b.d., i.e. before breakfast and before dinner ("Split mix" regimen).
3. *Multiple daily injections* – For achievement of more tight control of blood glucose which requires administration of at least 3 injections per day. These can be given with use of mixture of intermediate and short-acting insulins (pre-mixed insulin) in the morning before breakfast, with regular insulin before supper and intermediate acting at bedtime; or again a combination of regular and intermediate acting before dinner. Divide the total daily into 2 equal doses (following 1:1 transfer from basal insulin. Give half before breakfast and other half before dinner. The largest meal will require larger proportion of insulin. Reduce total dose by 20% if patient experiences recurrent hypoglycaemia.
4. *Insulin concentrations* – The insulins are available in many concentration. In India the commonly used is 40 U/mL. In United States, the insulin used is of concentration 100 U/mL. Worldwide insulin is available in a wider range of concentrations including U-40, U-80, U-100, U-500.
5. *Insulin purity* – The impurities which may be contained are proinsulin, insulin intermediates and contaminating proteins from islet tissue or exocrine pancreas such as glucagon, somatostatin and pancreatic polypeptides. Standard insulins currently have only 10 to 20 PPM of proinsulin and purified monocomponent insulins less than 1 PPM.

6. *Sites of injection* – The best sites are subcutaneous fat on abdomen, buttock, anterior thigh and dorsal area of arm. Insulin is rapidly absorbed if the extremity is subsequently exercised or with massage of local area, or increased local skin temperature.

Insulin Delivery Systems

Insulin Pens

A very important barrier in the use of conventional insulin delivery process which is time-consuming, inconvenient and painful. Insulin dosing via syringe is associated with a high risk of dosage errors. The pen devices have various advantages. The ease of insulin pens and the flexibility of incorporating insulin injections into the lifestyle can improve diabetic control with much less effect while maintaining the quality of life. It is also simpler for specific population to use (e.g. older adults, children and adolescents and pregnant women).

Types of Insulin Pens

1. *Reusable pens.* An insulin cartridge (called prefills), is inserted into the pen delivery chamber. This allows greater flexibility (i.e. changing types of insulin without the need to buy another pen, if prescription changes). Also they are designed for longer duration of use.
2. *Prefilled pens* contain a built-in single use insulin cartridge, hence requires no loading by the patients and is easy to use. These portable, durable and light weight delivery systems are particularly helpful for patients who have been handling the cartridges in reusable pens or those with busy schedules. The new generation flex pen have less injection force and an easy needle attachment with 'just twist' mechanism.

Continuous Insulin Infusion Systems in Type 2 Diabetes

Insulin pumps can be useful to mimic the physiological insulin secretion (Table 72). Pumps have the benefits of continuous subcutaneous insulin infusion (GSI) in selective patients with continuous glucose monitoring system (CGM) is a therapeutic option enabling diabetic patients to restructure life styles based on glycaemic pattern. Table 73 compares insulin pumps with pens.

Table 72: Indications for use of infusion pumps

High HbA1c levels despite multiple daily injections
Brittle diabetes
Frequent episodes of severe hypoglycaemia
Chronic kidney disease requiring kidney replacement
Elderly subject
Frequent travelers with varied food habits

Complications – of Insulin Therapy

- *Hypoglycaemia* – frequently encountered problem because of mismatch between timing of insulin, meals and exercise.
- *The counter-regulatory hormones* – Glucagon and epinephrine are of primary importance in the response to insulin-induced hypoglycaemia. Patients with diabetes progressively lose their counter regulatory hormone responses to hypoglycaemia. The first hormone to be lost is glucagon which is lost by 5 years of IDDM.
- *Nocturnal hypoglycaemia*

  Dawn phenomenon – Early morning glucose production by the liver is increased and sensitivity to action of insulin is decreased. Thus higher levels of insulin are required to maintain euglycaemia in early morning hours. This has been attributed to growth hormone surge which increases insulin resistance transiently.

  Somogyi effect – Increase in blood glucose value because of transient hypoglycaemia. It is mediated by increases in levels of circulating counter regulatory hormones.

  (See also later)
- *Insulin oedema* – The oedema may be present on feet and ankles or generalized anasarca. Insulin may act directly on kidneys reducing excretion of sodium and increasing retention of water.
- *Lipoatrophy and lipohypertrophy* – Seen with animal insulins. Lipoatrophy is localized loss or absence of subcutaneous fat at sites of frequent injections. The cause seems to be local immunologic reaction to impurities in insulin.

Table 73: Comparison of insulin pens vs insulin pumps

Insulin pens	*Insulin pumps*
Cheap	Very expensive
Easy to use and learn	Difficult to use and learn
Need to change cartridge and needle based on usage pattern	Need to change infusion set once in 3 days
Frequency of shot is more	Only one shot once in 3 days
Can incorporate any insulin (human, analogue, etc.)	Incorporates only fast-acting human insulin or rapid-acting analogue insulin
Bolus administration requires additional insulin shots	Any number of bolus doses can be delivered without pain of injection
	Risk of infection if infusion set not changed once in 3 days
	Overeating and frequent bolus insulin injection can lead to weight gain

Lipohypertrophy – is swelling of the subcutaneous fat. It is probably a direct effect of insulin on local tissue lipogenesis. Use of purified insulins prevents this occurrence.

- *Insulin allergy* – can be localized at site of injection or generalized. (a) Localized allergy – Patches of swelling and redness at site of injection, usually pruritic and often painful. (b) Generalized – Urticaria, pruritus, angioedema, rash, flushing, palpitations and bronchospasm. Acute anaphylaxis can occur but is extremely rare.
- *Obesity and weight gain* – Most of early weight gain following initiation of insulin therapy is due to rehydration and correction of catabolic state of poorly controlled diabetes, but subsequent chronic weight gain is two-third due to fat and one-third due to lean body mass.

Insulin Analogues

These modern insulins have been developed with an objective of overcoming the problems with conventional insulins. In general, they are considered more physiological, predictable and safe insulin preparations.

Modern Insulins

Rapid-acting

- Insulin lispro
- Insulin aspart
- Insulin glulisine

Long-acting

- Insulin glargine
- Insulin detemir

Premix

Biphasic insulin lispro

Clinical Efficacy of Rapid Acting Modern Insulins as Compared to RHI

- Better postprandial glucose control
- Good HbA1c control
- Less chances of hypoglycaemia
- Meal time flexibility

Use of Short-acting Modern Insulin in Special Situations

1. *Critical care* – Improved glycaemic control is associated with improved hospital outcome.
2. *Diabetic ketoacidosis* – Use of Aspart every 1–2 hr is safe and effective alternative to use of iv regular insulin.

Long-term efficacy – Treatment with rapid acting insulin analogue has shown an improvement in PPG and a reduction in the risk of CV events.

Kidney failure – Unaltered pharmacokinetics and safety profile in patients with various degrees of kidney dysfunction.

Gestational diabetes mellitus – Better control of PPG due rapid onset, more flexible regimen because it can be given pre-prandial as well as post-prandial, less hypoglycaemia and safe for both mother and fetus.

Analogues in insulin pumps – Replicating endogenous insulin production is the goal of treatment for DM. The two main methods of achieving this goal are continuous subcutaneous infusion (CSI) and multiple daily injections (MDIs) comprising basal and prandial injections. It has been shown that Lispro when used with external pump improves glycaemic control and stability with much lower doses than of insulin and dose increase frequency of hypoglycaemic episodes.

See Table 74 for Summary comparison of rapid acting insulin analogues.

Table 75 gives causes of recurrent hypoglycaemia in IDDM.

COMPLICATIONS

Metabolic Complications

Diabetic Ketoacidosis

Is a state of acidaemia induced by excess production of ketoacids. Dehydration and hyperglycaemia are the rule, lactic acidosis may also be present. See Table 76 for the precipitating causes of diabetic ketoacidosis.

Pathophysiology – Diabetic ketoacidosis is caused by severe insulin deficiency and is accentuated by excessive glucagon secretion. This leads to major clinical and laboratory abnormalities seen in diabetic ketoacidosis, which includes excess mobilization of free acids from adipose tissue, increased glucose production from the liver and impaired glucose uptake and utilization by muscle (Fig. 2).

The two major effects of uncontrolled diabetes are:

- Increased glucose production which causes hyperglycaemia, osmotic diuresis, electrolyte depletion and dehydration
- Increased ketogenesis, resulting in metabolic acidosis.

Diagnosis – The cardinal features are:

- Acidosis (arterial pH ≤ 7.3)
- Plasma anion gap (≥ 16 mmol/liter)

Table 74: Summary comparison of rapid acting insulin analogues

Diameter	*Glulisine*	*Lispro*	*Aspart*
Meal time flexibility	Pre as well as post-prandial administration	Pre as well as post-prandial administration	Pre as well as post-prandial administration
Blood glucose control	Similar control in comparison with Lispro	Similar to Glulisine	More than 10 mg/dl reduction as compared to Lispro
Hypoglycaemia	Maximum reduction in nocturnal hypoglycaemia upto 60% vs HI	Maximum reduction in nocturnal hypoglycaemia upto 68% vs HI	Maximum reduction in nocturnal hypoglycaemia upto 72% vs HI
Renal impairment	Conc. increases with moderate to severe renal dysfunction - upto 40%	Dose reduction required	Remains unaffected
Storage	Temp. 30°C	Up to 30°C	Up to 30°C
Shelf-life	24 months	27 months	30 months

Table 75: Recurrent hypoglycaemia in IDDM

1. Excessive or inappropriate dosage schedule.
2. Low renal threshold (renal glycosuria – dose monitoring with urine analysis).
3. Coexisting hypoadrenalism or hypopituitarism.
4. GI disease – Coeliac disease, diabetic gastroparesis.
5. Alcohol abuse.

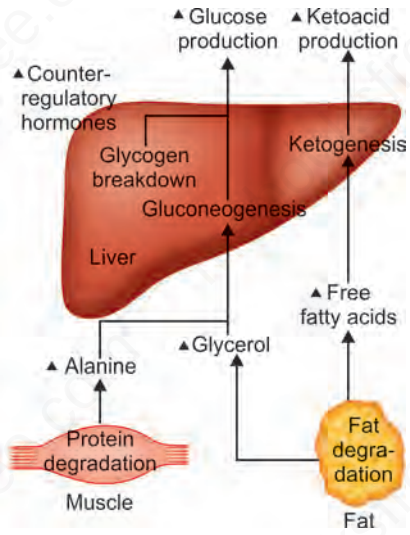


Fig. 2: Metabolic effects of severe insulin deficiency

- Serum ketone is positive
- Serum bicarbonate ≥ 15 mmol/liter
- Hyperglycaemia (plasma glucose ≥ 11.1 mmol/liter)

Differential Diagnoses of Comas in Diabetes: See Tables 77, 78 and 79.

Investigations

Blood glucose, urea and electrolytes (especially potassium), full blood count and blood gases. ECG should be monitored continuously for signs of hypokalaemia.

Table 76: Precipitating causes of diabetic ketoacidosis

1. Acute infection viral or bacterial single most common cause.
2. Omission of insulin or inadequate dosage.
3. Vomiting.
4. Diarrhoea.
5. Prolonged neglect of diabetes.
6. Indiscretions in diet.
7. Surgical operations.
8. Trauma.
9. Myocardial infarction.
10. Pregnancy.
11. Thyrotoxicosis.
12. Resistance to insulin.
13. Unnoticed interruption of insulin delivery in diabetics treated with continuous subcutaneous insulin infusion.

Management

See Table 80 for the management of diabetic ketoacidosis.

Complications of DKA

Iatrogenic complications

1. *Osmotic and volume disturbances*–Administration of insulin without sufficient fluids causes shift of water from extracellular space; further shrinking of extracellular fluid volume impairs blood flow to critical vascular beds, or precipitates vascular collapse. Similarly insufficient saline administration may also result in hypotension.
2. *Potassium disturbances* – Premature (before insulin has begun to act) and inappropriate potassium administration may cause fatal hyperkalaemia (cardiotoxicity) in early course of management. Glucose, insulin, and volume expansion with normal saline are potential modalities for lowering serum potassium;

Table 77: Differential diagnosis of coma in diabetes

Types of coma	*Blood glucose*	*Ketosis*	*Acidosis*	*Dehydration*
1. Ketoacidotic hyperglycaemia	+++	+++	+++	+++
2. Hyperosmolar hyperglycaemia state	+++	0	0	+++
3. Lactic acidosis	- to +++	0 to +	+++	0
4. Hypoglycaemic (see later)	Low	0	0	0
5. Kidney failure	+ to +++	0	++	0

Table 78: Differential diagnosis of ketoacidaemia from hypoglycaemic coma

	Diabetic ketoacidosis	*Hypoglycaemic coma*
History		
Precipitating cause	Infection, trauma, too little insulin	Undue exercise, missed meal, too much insulin or oral hypoglycaemic drug like glibenclamide.
Rate of onset	Slow, over a period of hours or days	Abrupt, minutes
Signs	Absent	Usually marked
Sweating	Marked	Nil
Dehydration	Rapid and deep (air hunger)	Stertorous
Respirations	Patient usually arousable (except in advanced case)	Coma often deep
Depth of coma		
CNS signs	Diminished	Usually brisk, extensor plantars
Reflexes	Absent	Common
Muscular twitchings	Absent	May occur
Convulsions	Yes	No
Acetone in breath		

Table 79: Differential diagnosis of diabetic ketoacidosis (DKA) and hyperosmolar non-ketotic coma

	DKA	*HONK*
Age and type of diabetes	Mostly in young Type 1, can occur in Type 2	Usually Type 2, > 40 yrs
Causes	Relative or absolute insulin deficiency	Multifactorial
Blood glucose (mg/dl)	>250	>600
Serum Na (mEq/L)	Normal or low	Usually high
Blood/urine ketones	++++	or trace (+)
Blood pH	<7.0	>7.3
Serum bicarbonate (mEq/L)	<15	>20
Serum osmolality	Variable	≥ 20 mosm/kg
Mortality	5–10%	30–50%
Subsequent course	Nearly always insulin dependent	Often controlled on diet alone Rarely need insulin

Table 80: Management of diabetic ketoacidosis

Admission

- Diagnosis suspected and confirmed immediately by blood glucose and ketone measurements
- Initial assessment of magnitude of dehydration, hyperosmolality, and acidosis
- Fluid loss measured by subtracting admission weight from last recently known stable weight
- Effective serum osmolality = 2 × [serum Na+ (mmol/liter) + serum K^+ (mmol/liter)] + serum glucose (mmol/liter) + urea (mmol/liter)]
- Initial assessment of serum potassium and kidney function.

Contd...

Contd...

- Evaluate patient for sepsis and/or precipitating illness

Hour 1

- *Fluid administration*
  - If strikingly hypovolaemic with low blood pressure and relative or absolute anuria, fluid administration should be normal saline and, if necessary, colloids; rate of administration should be that necessary to restore circulatory function
  - When blood pressure is normal and urine output adequate: fluid administration should be normal saline; rate of administration 1000 mL/hour
- *Insulin*

Contd...

Contd...

– Continuous intravenous infusion of regular insulin 5–10 units/hour or intramuscular regular insulin (20 units loading dose and 5 units/hour)
• *Potassium*
– Start intravenous potassium at 10–40 mmol/hour at initiation of insulin therapy if serum potassium is not > 5 mmol/liter and renal output is good. If patient is hyperkalaemic, temporarily delay intravenous potassium
• *Alkali*
– Sodium bicarbonate intravenously is seldom indicated, except in severe acidosis (pH < 7.0) with incipient circulatory collapse. Dose, if given, is 50–100 mmol/liter sodium bicarbonate given in 0.45% saline over 30–60 minutes. Additional K^+ must be given with bicarbonate therapy
Hour 2
• *Fluid administration*
• Continue normal saline at 500 mL/hour. Maintain calculated plasma osmolality > 285 mOsmol/liter throughout the first 12 hours. If serum Na^+ >150 mmol/liter switch to 0.45% saline.
• *Insulin*
• Check blood glucose and adjust insulin dose to maintain a fall of about 5 mmol/liter/hour. Do not allow blood glucose to fall below 11.1–14.0 mmol/liter. Anion gap should be decreasing and blood pH increasing
• *Potassium*
• Maintain serum potassium at 4.0–5.0 mmol/liter by continued addition of potassium to intravenous fluids
Hours 3-4
Continue as for hour 2
Observe for cognitive or neurological symptoms and continue to do so for 12 hours
Hours 5-8
• Fluid administration
– Normal saline 250 mL/hour. When blood glucose reaches 11.1–14.0 mmol/liter, change intravenous fluid to 500 mL/hour normal saline with 5% glucose
• Insulin
– Continue insulin at maintenance dose until ketoacidosis has cleared (blood pH > 7.35, serum ketones negative)
• Potassium
– Continue at 10–40 mmol/hour until ketoacidosis has cleared
• Phosphate
– Consider phosphate replacement at 6 hours if serum phosphate is < 2.0 mg/dL
Hours 8-24
• *Fluid administration*
– Continue intravenous repletion with 0.45% saline with or without 2.5% or 5.0% glucose as needed
• *Insulin*
– After ketoacidosis has cleared (blood pH > 7.35, serum ketones negative) switch to subcutaneous insulin and then stop intravenous or intramuscular insulin

hence, failure to administer potassium in later stages may cause fatal hypokalaemia in potassium-depleted patients.

3. *Hypoglycaemia and reappearance of ketosis* – During therapy of DKA, normalization of blood glucose is usually achieved sooner than reversal of ketoacidotic state. Because insulin therapy must be continued, hypoglycaemia develops unless glucose is given. Fingerstick glucose measurements should be done hourly for 4h, 2 hourly for next 4h, and 4 hourly till pt. improves. Glucose generally falls at rate of 50–100 mg/dL/h. Failure to maintain glucose and insulin treatment until ketones have been cleared and depleted glycogen stores restored, results in recurrence of ketosis.
4. *Cerebral oedema* – may rarely occur in children but is even rarer in adults. The condition should be suspected when a pt. with ketoacidosis begins to deteriorate 3 to 10 hours into treatment with increasing stupor or coma coupled with signs of raised intracranial pressure; an unexpected fever may also be an early sign. Osmotic disequilibrium between intracellular and extracellular fluids probably plays a role. Tr. – Mannitol 20% iv 1.5–2 mL/kg body wt. over 15 minutes and dexamethasone 10 mg iv followed by 4mg in q6h. Clinical response will be seen in 12–24 h.
5. *Hypocalcaemia* – may develop during phosphate replacement.

Non-iatrogenic complications

1. *Infection* – Although leucocytosis may occur in DKA in absence of infection, fever generally indicates infection and demands careful search for pneumonia, pyelonephritis and septicaemia. A rare ketoacidosis-associated infection is mucormycosis of paranasal sinuses with facial pain, bloody nasal discharge, orbital swelling, blurred vision and impaired consciousness. Tr. – Broad spectrum antibiotics. Blood, urine and throat cultures should be taken prior to giving antibiotic.
2. *Vascular thrombosis* – Combination of volume contraction, low cardiac output, increased blood viscosity, underlying atherosclerosis, direct endothelial damage due to hyperosmolar milieu, and changes in clotting factors and platelet function predispose to thrombosis.
3. *Respiratory distress syndrome* – Hypoxia and ARDS may develop in course of therapy of DKA hyperosmolar coma. Clinical picture is characterized by unexplained hypoxaemia and dyspnoea in absence of any underlying pulmonary/cardiac disease.
4. *Pancreatitis* – Acute abdominal pain is a common presentation of DKA, and resolves rapidly on therapy.

Specific etiologies can be gastroparesis, ischaemic bowel, and cholecystitis. Raised serum amylase is observed in 80% of cases. It may represent pancreatic damage (hypertonicity and hyperperfusion); in some instances, it is subclinical.

5. *Myocardial infarction* – can precipitate or complicate DKA, it is a major cause of morbidity.
6. *Hyperlipidaemia* – Severe hypertriglyceridaemia (triglycerides > 1000 mg/dl) is seen in about 10% which on follow-up resolve in 70% of cases. The abnormality is related to acute metabolic changes in DKA.

Hyperosmolar Hyperglycaemic State

Generally occurs in elderly often in non-insulin dependent or new diabetic. Precipitating factors – include infection, myocardial infarction and treatment with drugs such as thiazides, steroids and diphenylhydantoin. The situation may be exaggerated by drinking large quantities sugar containing fluids from excessive thirst.

Clinical features – It is characterised by severe dehydration, hyperglycaemia and absence of ketoacidosis.

- **Laboratory findings** – Blood glucose >50 mmol/liter (900 mg/mL), plasma urea > 120 mg/100 mL and often raised plasma osmolality (often more than 360 mOsmol/kg).
- **Management**– *IV fluids*: Start 1 L 0.9% NaCl/hr initially. Hypovolaemic shock – 0.9% NaCl (1 L/h) and/or plasma expanders
  - Mild hypotension – Evaluate serum Na^-
  - High: 0.45% NaCl (4–14 mL/kg/h) depending on state of hydration
  - Low: 0.9% NaCl (4–14 mL/kg/h) depending on state of hydration

When serum glucose reaches 300 mg/dL, change to 5% dextrose with 0.45% NaCl and decrease insulin to 0.05-01 U/kg/h to maintain serum glucose between 250-300 mg/dL until plasma osmolality is ≥ 315 mOsm/kg and patient is mentally alert.

Insulin

Regular 0.15 U/kg as iv bolus followed by 0.1 U/kg/h iv infusion

Check serum glucose hrly. If it does not fall by 50 mg/dL in first hr, then double the insulin dose hrly until glucose falls at a steady hrly rate of 50–70 mg/dL

Check electrolytes, BUN, creatinine and glucose every 2–4 h until stable. If patient is NPO, continue iv insulin and supplement with sc regular insulin as needed. When patient can eat, initiate sc insulin or previous treatment regimen and assess control.

Potassium

If initial serum K is < 3.3 mEq/L, hold insulin and give 40 mEq K (2/3 as KCL and 1/3 as KPO_4) until K ^{3}3.3 mEq/L.

If initial serum K ≥ 5, do not give K but check potassium every 2 hrs.

If initial serum K ≥ 3.3 but < 5 mEq/L, give 20–30 mEq in each liter of iv fluid to keep serum K at 4-5 mEq/L.

Lactic acidosis **–** Rare cause of severe metabolic acidosis. Caused by excess lactate production and/or inadequate utilization. It may be precipitated by metformin, or another systemic disorder, e.g. diabetes, liver or renal failure, pancreatitis or leukaemia. Evidence of cardiovascular collapse is usually evident.

Management – is mainly supportive. Large doses of soda bicarb are required to maintain normal pH, until the primary cause is removed. Peritoneal or hemodialysis may be necessary to remove excess sodium. Blood transfusion may be helpful if severe hypotension.

Hypoglycaemic Coma (Refer)

Non-metabolic Complications

The 'triopathy' (retinopathy, neuropathy and nephropathy) are the classical late complications of diabetes mellitus.

Diabetic Retinopathy

1. Background diabetic retinopathy – includes hemorrhages and microaneurysms in retina, together with exudates. Visual acuity is normal.
2. Pre-proliferative retinopathy – is a development of background retinopathy. Capillary closure occurs leading to retinal ischaemia.
3. Proliferative retinopathy – is characterised by growth of new vessels on optic disc and iris. Hemorrhage occurs initially in subhyaloid space but progresses to involve the vitreous gel, leading to poor vision. Untreated disease may result in traction retinal detachment.
4. Proliferative disease – of the iris (rubeosis iridis) may occur.
5. Maculopathy – due to hemorrhage, oedema of macula, ischaemia and proliferation of macula.

Prevention - American Diabetes Association (ADA) recommends the following = ophthalmologic examination schedule: (1) individuals with type 1 DM should have an initial eye examlnation within 5 Years of diagnosis (2) individuals with type 2 DM should have an initial eye examination at the time of diabetes diagnosis, (3) women with DM who are; pregnant or contemplating pregnancy

should have an eye examination prior to conception and during the first trimester and (4) if eye exam is normal, repeat examination in 2–3 years is appropriate.

Tr. (a) Proliferative retinopathy – Panretinal photocoagulation. (b) End-stage proliferative retinopathy – Pars plano vitrectomy. (c) Rubeosis iridis – Photocoagulation. (d) Maculopathy – Grid treatment to areas of thickening. If advanced macular oedema generalised grid therapy, with photocoagulation applied to macula.

Diabetic Nephropathy

Major cause of premature death, principally from end-stage kidney disease and cardiovascular disease (Table 81). See Table 82 for the risk factors and Table 83 for the staging of diabetic nephropathy.

Pregnancy and Proteinuria in Diabetes

Development of microalbuminuria or macroalbuminuria in a diabetic woman carries the risk of pre-eclampsia.

Nephropathy in Type 2 DM – is largely disease of older age, with associated obesity, hypertension and dyslipidaemia and high rates of cardiovascular disease that restrict manifestations of diabetic kidney disease.

Renal medullary necrosis results from ischaemia to the medulla and papilla. Patient has flank pain, hematuria and fever. Urinanalysis shows red and white blood cells, bacteria and papillary fragments.

Renal tubular acidosis manifests as hyperkalaemic and hyperchloraemic metabolic acidosis.

Nephropathy in type 2 Diabetes has more similarities than differences in T1DM. Hyperfiltration is less common. Microalbuminuria might not be as specific for diabetic kidney disease.

Tr. – ACE inhibitors reduce the rate of progress from micro-to macroalbuminuria and can slow the decline in GFR in patients with microalbuminuria. In addition ACEIs tend to reduce severe CVD (cardiac infarction, stroke). ARBs have a smaller magnitude of rise in potassium compared to ACEIs. In patients unable to tolerate ACE inhibitor and/or ARBs, use of non-DCCBs, β-blockers or diuretics can be considered for control of BP.

Diabetic Foot

Risk factors: (a) Evidence of neuropathy. (b) Evidence of ischaemia. (c) Foot deformities. (d) Callus at pressure areas. (e) Previous history of foot ulcers. (f) Impairment of sight (when attempting self-care). (g) Elderly.

See Table 84 for the grading of diabetic foot ulcers.

Tr. – High risk patients should be advised to wash and inspect the feet daily, use creams or lotions to prevent dry skin/callus formation, avoid walking barefoot and avoid thermal injuries, seek medical attention for any injury/discomfort, and avoid self-treatment of corns, calluses or other disorders.

Diabetic Neuropathy

See Table 85 for the types of diabetic neuropathy.

(a) ***Sensorimotor neuropathy*** – 1. Acute – Neuropathy is symmetrical and predominantly sensory. Symptoms Pain, stabbing or burning, particularly on soles of feet and shins. (a) Hyperaesthesia. (b) Paraesthesiae and feeling of numbness. 2. Chronic – may take years to develop, and nerve function in most cases unlikely to improve. Treatment – Tricyclic antidepressants e.g. Amitryptiline 25–50 mg at bedtime may provide relief from pain.

(b) ***Autonomic neuropathy***.

See Table 86 for the clinical manifestations of autonomic neuropathy.

(c) ***Diabetic mononeuropathy*** – (a) Entrapment neuropathy (median carpal tunnel syndrome, usually bilateral, or of lateral cutaneous nerve of thigh). (b) Spontaneous mononeuropathy – Cranial nerves 3rd and 6th are most often involved. Onset is sudden but recovery occurs in most patients after weeks or months. (c) External pressure palsies – e.g. of radial, ulnar and peroneal nerves.

Table 81: Definitions of abnormalities in albumin excretion

Category	24-h urinary albumin exertion rate	Overnight urinary albumin excretion rate	Albumin: creatinine ratio
Normal albuminuria	<30 mg/day	<20 µg/min	<2.5 mg/mmol (for men) <3.5 mg/mmol (for women)
Microalbuminuria	30–300 mg/day	20–200 µg/min	2.5–25 mg/mmol (for men) 3.5–25 mg/mmol (for women)
Macroalbuminuria (overt nephropathy)	>300 mg/day	>200 µg/min	>25 mg/mmol

Table 82: Risk factors for diabetic nephropathy
• Hyperglycaemia
• Hypertension
• Baseline urinary albumin excretion
• Increasing age
• Duration of diabetes
• Presence of retinopathy
• Smoking
• Raised cholesterol and triglyceride
• Male gende

Table 83: Stages of Nephropathy in type 1 DM
• *Stage 1*: Hyperinflation is associated with increased GFR.
• *Stage 2*: Silent stage. Absence of any kidney dysfunction clinically.
• *Stage 3*: Microalbuminuria or stage of incipient nephropathy. Urinary albumin excretion rate in range of 30 to 300 mg/24 hrs. Concomitant increase in systolic and diastolic BP.
• *Stage 4*: Macroalbuminuria. Urinary albumin excretion > 300 mg/24 hrs. If left untreated, BP continues to rise, accelerating decline in GFR.
• *Stage 5*: Uremia and end stage kidney disease.

Table 84: Grading of diabetic foot ulcers	
Grade 0	High-risk foot, no ulcers
Grade 1	Superficial ulcer, skin deep
Grade 2	Deeper ulcer, usually with infection/cellulitis, no bone involvement
Grade 3	Osteomyelitis and foot ulceration
Grade 4	Localised gangrene (toes, forefoot or heel)
Grade 5	Gangrene of entire foot

Table 85: Diabetic neuropathy
(a) Sensorimotor neuropathy – Acute – Chronic
(b) Autonomic neuropathy
(c) Diabetic mononeuropathy
(d) Proximal motor neuropathy(Diabetic amyotrophy)

(d) ***Proximal motor neuropathy (Diabetic amyotrophy)*** – Cl. Fs. – Acute onset in type 2 poorly controlled diabetes with markedly elevated HbA1c. (a) Presents with severe pain, paraesthesia, hyperpathia in upper legs, and weakness and muscle wasting, especially of quadriceps. (b) Skin tenderness over anterior aspects of the thighs and weakness of hip flexion in one or both legs. (c) Knee jerks may be absent. (d) Often complicated by development of contralateral pelvic girdle weakness, wasting, weight loss, incontinence and impotence. (e) Occasionally associated with extensor plantar response and/or elevated CSF protein. (f) Excellent long-term prognosis, at least partial recovery within 1–2 years, but recurrence not uncommon.

Skin Disorders

1. *Diabetic dermopathy* (skin spots, pigmented pretibial patches). Bilateral multiple hyperpigmented macules in pretibial areas. Lesions may also appear on forearm, and anterior surface of lower thigh. Lesions ultimately evolve into shallow pigmented scars.
2. *Vascular abnormalities.* Small arterial involvement may lead to slow healing leg ulcers.
3. *Nerve-related problems.* Motor nerve damage leads to risk of ulcers on feet.
4. *Infections.* Cutaneous manifestations may be due to vascular, nutritional or metabolic disturbances –

Table 86: Clinical manifestations of diabetic autonomic neuropathy
Cardiovascular
• Painless myocardial infarction
• Orthostatic hypotension
• Tachycardia
Gastrointestinal
• Constipation
• Diarrhoea
• Oesophageal dysfunction
• Faecal incontinence
Gastroparesis
• Genitourinary
• Erectile dysfunction
• Neurogenic bladder
• Retrograde ejaculation
• Cystopathy
Metabolic
• Hypoglycaemia unawareness
• Hypoglycaemia unresponsiveness
• Argyll Robertson pupil
• Sweating disturbances
• Areas of asymmetrical anhidrosis
• Gustatory sweating
• Heat intolerance

(a) Bacterial - Folliculitis, furuncle, carbuncle, styes, paronychia, cellulitis

(b) Fungal - Vulvovaginitis, balanitis, intertrigo

(c) Viral - Herpes zoster.

5. *Necrobiosis lipoidica diabeticorum (NLD)* is one of the best cutaneous markers for DM. It presents with well-circumscribed erythematous papules, which develop into large irregularly delineated plaques, with a waxy, yellow centre. Also the epidermis becomes thin and transparent, allowing underlying vasculature to become visible.
6. *Insulin resistant disorders.* (a) Acanthosis nigricans. A close association exists between AN, obesity, and insulin resistance. Presence of AN on neck and medial thigh is more commonly associated with obesity. Conversely in nonobese patients, lesions may occur in axillary region. (b) Bullosis diabeticorum. Bullae appear spontaneously, usually on feet and toes, and occasionally on hands and fingers. They often occur in patients with diabetic neuropathy.
7. *Atherosclerosis.* It causes the skin of legs to become hairless, thin and shiny. Toenails thicken and discolour.
8. *Eruptive xanthomatosis.* The condition is caused by long-term high blood glucose levels. It consists of firm, yellow, pea-like lesions. Each lesion has a red halo and may itch. Like blisters of DM, lesions usually disappear when blood glucose and cholesterol levels are in a healthy range.
9. *Digital sclerosis* occurs more commonly in type 1 DM. Skin on the back of the hands becomes tight and thick. Sometimes skin on toes and forehead also becomes thick. Finger joints can also become stiff, so that patient is unable to approximate palmarsurfaces of fingers and palms – 'Prayer sign' (Fig. 3).
10. *Granuloma annulare.* Most common form is localized annulare. The generalized form is more prevalent and presents in the form of annular or arciform plaques, that begin as red or reddish-brown papules symmetrically spread across upper trunk, neck, arms, and occasionally legs.
11. *Allergic skin reactions* can occur in response to drugs.
12. *Dry skin*. Rough, dry and scaly skin affects most individuals over 60. It can be found on the legs, feet, hands and or face. In more serious cases the skin loses its suppleness, and can crack and become inflamed.

Charcot's neuroarthropathy is a rare and disabling condition affecting the joints and bones of the feet. Features for development of this condition are together with autonomic dysfunction with increased flow of blood flow to the foot. A unilateral swollen hot foot with neuropathy must be considered to be Charcot's foot until proved otherwise.

Fig. 3: Positive prayer sign

Endothelial Dysfunction in Diabetes

Endothelial dysfunction is believed to be the earliest functional abnormality in blood vessels in diabetes. Several therapies have been shown to ameliorate this, namely exercise and weight loss, lipid lowering, anti-oxidants, PPAR-X and agonists reducing homocysteine levels, aspirin reducing hyperglycaemia and more recently nitric oxide co-factors such as tetrahydrobiopetrin and modulation of insulin resistance.

Microvascular Complications in Diabetes

Hypercoagulable state as indicated by decreased fibrinolysis and increased coagulability is responsible factor for their developments.

Gastroparesis in DM – Delayed gastric emptying in absence of gastric outflow obstruction. It can lead to worsening of glycaemic control and malnourishment.

Table 87 gives proposed mechanisms by which hyperinsulinaemia contributes to hypertension.

Carotid Intima-media Thickness in Type-2 DM

CIMT measurements is an effective, noninvasive technique which can assist in identifying patients with diabetes who are at higher risk of developing microvascular and macrovascular complications.

Somogyi phenomenon. (Post-hypoglycaemic hyperglycaemia) refers to rebound hyperglycaemia after an episode of hypoglycaemia as a result of counter regulatory hormone release. It manifests as morning fasting hyperglycaemia in response to undetected nocturnal hypoglycaemia. The subtle clinical signs of which are mild nocturnal sweating, morning headache and hypothermia. The significance of this phenomenon is that correction of morning hypoglycaemia depends on reducing and not increasing the evening dose of intermediate-acting insulin.

Dawn phenomenon. In this, there is fasting hyperglycaemia but no hypoglycaemia. This is likely to be due to nocturnal surge for GH release or increased clearance of insulin in the morning. It can be confirmed and differentiated from Somogyi phenomenon by observing hyperglycaemia at 3am and in morning fasting state. The aim is to demonstrate that correcting of fasting hyperglycaemia is by increasing and not decreasing the dose of insulin.

FIBROCALCULOUS PANCREATIC DIABETES

FCPD is a type of diabetes secondary to Tropical Chronic Pancreatitis (TCP). TCP is a juvenile form of non-alcoholic chronic calcific pancreatitis peculiar to tropical countries.

Etiology – Age – Majority between 10–40 years. Sex– Males predominate.

Clinical Features

1. *Abdominal pain* usually occurs several years before onset of diabetes and usually disappears by the time that diabetes is manifest. Pain usually severe, epigastric and with periods of remission and exacerbation. It radiates to back on either side and is relieved by stooping forward or lying in a prone position. 2. *Diabetes* is usually severe and most patients require insulin. 3. *Steatorrhoea* may occur. 4. *Others* – Extreme emaciation, peculiar cyanotic hue of lips, bilateral parotid enlargement and abdominal distension.

Table 87: Proposed mechanisms by which hyperinsulinaemia contributes to hypertension

Vasodilation
Increased sympathetic activity directly and from vasodilatation
Increased renal sodium/hydrogen exchange
Lower free acids stimulating aldosterone secretion
Vascular smooth muscle proliferation
Atherosclerosis increasing vascular rigidity

Investigations

1. *Plain X-ray of abdomen* – Presence of pancreatic calculi, mostly to right of first and second lumbar vertebrae, may occasionally overlap the spine.
2. *Ultrasonography* – Pancreas appears hyperechoic with irregular margins, the duct is irregularly dilated and shows stones in the lumen.
3. *CT scan* – Pancreatic mass is preserved in early stages, varying degree of atrophy in more advanced disease. In extreme cases little pancreatic parenchyma is visible, its place being taken by a 'bag of stones'. Pancreatic duct appears irregularly filled with stones in the lumen.
4. *Pancreatic function tests* – abnormal.

Treatment

(a) *Of diabetes* – Insulin is required in more than 80% of cases. Upto 20% respond to oral hypoglycaemic agents (usually sulphonylureas). (b) *Oral pancreatic enzymes* – for steatorrhoea (c) *Surgery* – if severe and intractable pain – Lateral pancreato jejunostomy. Pancreatectomy might be needed.

8. HYPOGLYCAEMIA

A deviation below normal fasting range of blood sugar (2.5 mmol/liter). It may be asymptomatic, mild (recognised and corrected by the patient), severe, or may present as coma. See Table 88 for the Clinical classification of hypoglycaemia.

HYPOGLYCAEMIA WITHOUT HYPERINSULINAEMIA

1. Postprandial.
2. Alcohol ingestion.
3. Starvation, prolonged exercise, infection (e.g. P. falciparum).
4. Non-islet cell tumors (release IGF-II) – e.g. Hepatoma, adrenal carcinoma, mesothelioma, fibrosarcoma.
5. Iatrogenic – Oral hypoglycaemic drug, postpolygastrectomy (late dumping), salicylism (in children), propranolol (inhibits hepatic glycogenolysis).

Insulin-induced hypoglycaemia – After 10 years or more of diabetes, in some patients the adrenergic features become less marked, and neuroglycopenic symptoms are more prominent. Beta-blockers like propranolol can impair warning symptoms as also switch over from animal to human insulin.

Table 88: Clinical classification of hypoglycaemia

1. *Postprandial (reactive) hypoglycaemia –*
Endogenous hyperinsulinism
– Insulin antibodies
– Noninsulinoma pancreatogenous hypoglycaemia
Congenital deficiencies of enzymes of carbohydrate metabolism
– Hereditary fructose intolerance
– Galactosaemia
Others
– Alimentary hypoglycaemia
– Idiopathic (functional) postprandial hypoglycaemia
2. *Postabsortive (Fasting) hypoglycaemia**
Drugs
– Insulin or insulin secretagogues
– Sulfonylureas
– Quinine
– Pentamidine
– Salicylates, sulfonamides (rarely)
Critical illness
– Hepatic, kidney or cardiac failure
– Sepsis
– Malaria
– Inanition
Hormonal deficiencies
– Cortisol or growth hormone or both
– Glucagon and epinephrine (in insulin dependent DM)
Endogenous hyperinsulinism
– Insulinoma
– Noninsulinoma
– Autoimmune hypoglycaemia
– Antibodies to insulin
– Antibodies to insulin receptor
Others
– Non-beta-cell tumors
– Hypoglycaemia of infancy and childhood

*Precipitated by deprivation of food for few hours or longer. Fasting hypoglycaemia indicates an identifiable underlying disease, while reactive post-prandial hypoglycaemia occurs in absence of organic disease.

SYMPTOMS

Sympathoadrenal symptoms are caused by increased activity of the autonomic nervous system and may be triggered by a rapid fall in glucose concentration. *Neuroglucopaenic symptoms* are caused by cerebral glucose deficiency and require an absolutely low level of glucose (Table 89).

Table 89: Symptoms of hypoglycaemia

Autonomic	*Neuroglucopaenic*
• Sympathetic	Dizziness
– Tremor	Confusion
– Sweating	Tiredness
– Palpitation	Difficulty in speaking
– Anxiety	Inability to
– Nausea	concentrate
– Warmness	Headache
– Shivering	Amnesia
• Parasympathetic	Shivering
– Pallor	Drowsiness
– Paraesthesia	Blurred vision
– Hunger	Drowsiness
– Sweating	Seizures
	Coma

Large doses of glucose should be avoided in NIDDM to avoid possibility of a resultant hypoglycaemia stimulating a further insulin response.

Sequelae – Prognosis for recovery of cerebral function deteriorates with increasing duration of coma. Prolonged severe or recurrent hypoglycaemia usually leads to permanent cerebral damage or dementia.

DIAGNOSIS

A. Of Hypoglycaemia state

1. Suggestive history.
2. Dramatic response to IV glucose during attack.
3. Low plasma glucose level during attack (<94 mg/dL).
4. C-peptide concentrations >200 pml/L

B. Of the cause

Fasting attacks:

(a) *Clinical* – Exclude hypopituitarism, Addison's disease, liver cirrhosis or failure, sarcoma (radiograph of chest and abdomen), alcohol ingestion after fasting, self-administration of insulin or sulphonylurea.

(b) *Investigations for insulinomas* – (i) Overnight fasting plasma glucose and insulin measurements – will demonstrate spontaneous hypoglycaemia and raised plasma insulin (Normal range 3–13 mU/liter at normal fasting plasma glucose concentration). (ii) Plasma C-peptide measurements – Low plasma C-peptide with high plasma insulin. (iii) Plasma proinsulin measurements – High fasting plasma pro-insulin.

Localization – Insulinomas tend to be small. CT scan can detect 70–80 and MRI about 85%. Transabdominal ultrasound identifies many insulinomas and endoscopic ultrasound has sensitivity of about 90%. Selective pancreatic arterial calcium injections, with end point of sharp increase in hepatic venous insulin levels but is an invasive procedure. Intraoperative pancreatic ultrasonography invariably localizes insulinomas that are not palpable by the surgeon.

Tr. – Surgical resection is curative. Medical therapy for unresectable insulinomas includes administration of diazoxide or octreotide.

(c) *Self-administration of insulin* – (i) Insulin antibodies. (ii) During spontaneous hypoglycaemia low plasma C-peptide with high plasma insulin.

(d) *Sarcoma* – Spontaneous hypoglycaemia with low plasma insulin and no ketosis.

MANAGEMENT

1. *Acute attack* – Administration of rapidly absorbable carbohydrate. (a) In mild reaction – orange juice (100 mL) or corn syrup or candy taken orally sufficient. (b) *In unconscious or uncooperative patients* 50 mL of 50% glucose i.v. If vein not available Glucagon 1 mg s.c. or i.m. will cause sufficient increase in blood sugar to allow the patient to become rational and cooperative. The hyperglycaemic effect is however transient and supplementary carbohydrate must be given to prevent relapse. It is ineffective in hypoglycaemia induced by alcohol. When recovery is slow, e.g. after overdose of insulin or sulphonylurea therapy, constant infusion of 10-20% dextrose is given to maintain the blood sugar.
2. *Conservative treatment and prevention of acute attacks* (a) Diet – carbohydrate not more than 150 gms in slowly absorbable form like cereals, bread, fruits and vegetables. Liberal protein because glucose derived from it is liberated slowly; fat to make up calories. In hepatogenic type bed-time meal to prevent early morning hypoglycaemia. (b) Restriction of physical exercise.
3. *Surgical measures* – Removal of islet cell tumors, or partial resection of pancreas in: (a) fulminating cases where convulsions are not controlled by glucose. (b) Severe chronic cases not controlled by diet. (c) Patients with marked, neuropsychiatric symptoms.
4. *Drugs* – (a) Glucagon – The efficacy depends on size of hepatic glycogen stores. The drug has little effect on blood glucose in patients who have been fasting or are hypoglycaemic for long periods. Diazoxide and Octreotide may be used to control symptoms while the patient is awaiting surgery or when the patient is not a candidate for surgery.

9. MULTIPLE ENDOCRINE NEOPLASIA MEN

MEN is characterised by occurrence of tumors involving two or more endocrine glands in a single patient. The MEN syndromes are inherited as autosomal dominant disorders, first degree relatives have about 50% risk of developing the disease.

FORMS OF MEN

There are two major forms: MEN type I and type II. Each form is characterized by development of tumors within specific endocrine glands. Clinical manifestations are related to the sites of tumors and to their products of secretion (Table 90).

MTC-ONLY – In this variant, medullary thyroid carcinoma is the sole manifestation of the syndrome.

Genetic testing – Identifies the 50% of family members who do not have inherited the mutation and who do not have to undergo further screening, for family members who have inherited the mutation and are at a high risk of developing tumors, there are two clinical approaches –

(a) Continued testing of calcitonin release following pentagastrin stimulation. This usually delays total thyroidectomy until 10–13 years of age.

(b) Total thyroidectomy is advised on the sole basis of the abnormal genetic test, at the age of 5 years; the earliest age at which metastasis in MEN2α has been reported and total thyroidectomy at an earlier age has been recommended.

10. CARCINOID SYNDROME

Carcinoid syndrome is a constellation of symptoms, most obviously flushing and diarrhoea, caused by the release of hormones and other substances from a carcinoid tumor, a type of neuroendocrine tumor (Table 91).

Diagnosis – (a) Estimation of 24-hour urinary excretion or 5-HIAA, the breakdown product of serotonin. Circulating chromogranin A levels are also raised. (b) Routine imaging (chest radiography/CT and hepatic ultrasonography or CT/MRI) reveals presence of hepatic secondaries and bronchial primaries (Fig. 4). (c) Isotope imaging using somatostatin may clarify the distribution of the disease particularly hepatic deposits (nodal disease). Radio-labelled MIBG is actively metabolized by some tumors and may also show their distribution.

Management – (a) Drug therapy – Injections of somatostatin reduce tumor size in a small proportion of patients.

Table 90: Multiple endocrine neoplasia syndromes

Type	*Tumors*	*Biochemical features*
MEN1	*Parathyroids*	Hypercalcaemia and ↑ PTH
	Pancreatic islets Gastrinoma Insulinoma Glucagonoma VIPoma PPoma	↑ Gastrin and ↑ basal gastric acid output Hypoglycaemia and ↑ insulin Glucose intolerance and ↑ glucagon ↑ VIP and WDHA ↑ Pancreatic polypeptide
	Ant. Pituitary Prolactinoma GH-secreting ACTH-secreting	 Hyperprolactinaemia ↑ GH Hypercortisolaemia and ↑ ACTH
	Associated tumours Adrenal cortical Carcinoid Lipoma	 Hypercortisolaemia or primary hyperaldosteronism ↑ 5-HIAA Nil
MEN2a	*Medullary thyroid carcinoma* *Pheochromocytoma* *Parathyroid*	Hypercalcitoninaemia ↑ Catecholamines Hypercalcaemia and ↑ PTH
MEN2b	*Medullary thyroid carcinoma* *Pheochromocytoma* *Associated abnormalities* Mucosal neuromas Marfanoid habitus Medullated corneal nerve fibres Megacolon	Hypercalcitoninaemia ↑ Catecholamines

PTH: parathyroid hormone. VIP: Vasoactive intestinal peptide. WADHA: Watery diarrhoea, hypokalaemia and achlorhydria. 5-HIAA: 5-hydroxyindoleacetic acid.

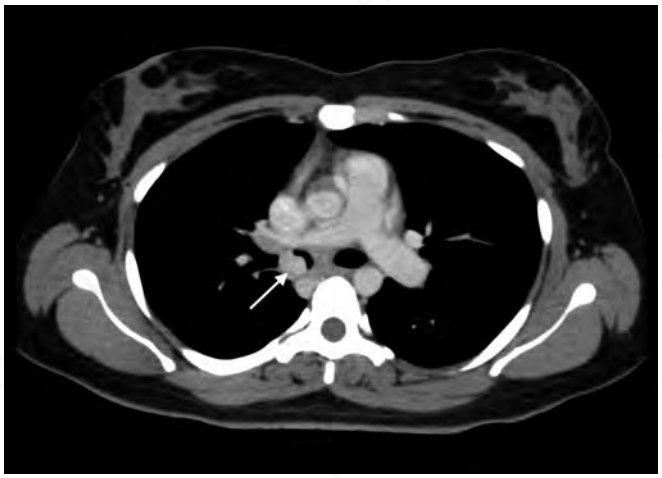


Fig. 4: Right bronchial carcinoid (arrow)

Table 91: Clinical features of carcinoid syndrome

- Flushing
- Diarrhoea
- Hepatomegaly
- Abdominal pain
- Bowel obstruction
- Others
  - Hemoptysis
  - Wheeze
  - Sweating
  - Palpitations

Octreotide is given thrice daily s.c. or in long-acting depot preparations. (b) Non-surgical debulking – (i) Transarterial embolization (cutting off the arterial blood supply on which the secondary deposits depend) can be performed when the portal circulation remains intact. Prophylaxis with high octreotide and antibiotics is necessary. (ii) Radioisotope therapy (iodine-labelled or Yttrium-labelled) somatostatin can be targeted to extensive tumor deposits if initial investigations show that the tumor accumulates the isotope.

Table 92: Causes of precocious puberty

True precocious puberty
Gonadotropin-releasing hormone dependent
• Idiopathic
• Secondary – Cerebral palsy/hydrocephalus – Tumor masses in hypothalamic region – Head trauma – Chronic inflammatory conditions – Radiotherapy – Sexual abuse – Adoption-related
Gonadotropin-releasing hormone independent
• McCune-Albright syndrome • Testotoxicosis
Precocious breast development
• Premature thelarche • Thelarche variant • Hypothyroidism
Virilization (Pubic, axillary hair development)
• Adrenarche • Congenital adrenal hyperplasia • Cushing's disease • Adrenal tumors
Others
• Gonadotropinsecreting or sexsteroid secreting tumors • Exogenous steroids

Table 93: Endocrine causes of hypertension

Mineralocorticoid excess states • Low renin, high aldosterone • Primary aldosteronism
Low renin, low aldosterone • Congenital adrenal hyperplasia • Liddle's syndrome • Apparent mineralocorticoid excess • Liquorice or carbenoxolone ingestion
Mineralocorticoid/glucocorticoid excess states: • Cushing's syndrome (particularly ectopic adrenocorticotropin syndrome) • Steroid therapy (glucocorticoid/mineralocorticoid activity)
Pheochromocytoma
Miscellaneous • Acromegaly • Primary hyperparathyroidism

11. MISCELLANEOUS

PANCREATIC TRANSPLANTATION

Indications – (a) Patients who have Type-1 DM with kidney failure and who are therefore candidates for kidney transplantation. (b) Failure of standard therapy and episodes of hypoglycaemia unawareness.

Relative contraindications – Age >55 and significant atherosclerotic cardiovascular disease. Cell and islet can be cryopreserved to optimize timing of transplantation.

Pancreatic islet cell transplantation is less invasive and islets can be cryopreserved to optimize timing of transplantation.

CHAPTER

7

Neurology

1. INVESTIGATIONS IN NEUROLOGY

NEURORADIOLOGY

Skull X-ray

CT scanners and MRI produce bone images much superior to plain radiographs. Still plain X-rays can be used for conditions listed in Table 1.

Spine X-ray

(a) *Antero-posterior view* – Pedicle erosion with or without paraspinal mass suggests malignant extradural tumour. Osteosclerotic myeloma and POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin Changes) associated with demyelinating neuropathy similar to CIDP (Chronic Inflammatory Demyelinating Polyradiculopathy).

(b) *Lateral view* – (i) Collapse of vertebral body suggests malignant infiltration. (ii) 'Scalloping' of posterior surface of vertebral body indicates longstanding intradural lesion. (iii) Narrow disc space, narrow canal and hypertrophic facet joints disc disease or lumbar spinal canal stenosis. If disc space is destroyed infection is more likely.

(c) *Oblique views* – (i) Expansion of intervertebral foramina suggests neurofibroma. (ii) Narrowing from osteophytic encroachment indicates possible root compression.

Table 1: Utility of lain X-ray of skull

1. *Fractures* – in head injury patients.
2. *Bone erosion* – (a) Focal, e.g. pituitary fossa. (b) Generalized, e.g. Multiple myeloma.
3. *Bone hyperostosis* – (a) Focal, e.g. Meningioma. (b) Generalized, e.g. Paget's disease.
4. *Abnormal calcification* – (a) Tumors, e.g. meningioma, craniopharyngioma. (b) Aneurysm wall.
5. *Midline shift* – if pineal calcified.
6. *Signs of increased intracranial pressure* – Erosion of posterior clinoids.
7. *Configuration* – Platybasia, basilar impression.

CT Scanning

Brain – Abnormalities are inferred from alterations in tissue density and displacement of normal structures (Fig. 1).

CT with contrast media – Contrast media are used to highlight regions with breakdown of blood barrier which leads to enhancement (demyelination, encephalitis, granuloma, abscess, tumour, metastasis). The extent of enhancement also reflects relative cerebral vascularity, which is increased in some lesions (e.g. A-V malformations) and reduced in areas of acute infarction. Intrathecal contrast medium is used for CT myelography or cisternography. CT is more sensitive than MRI to intracranial calcification and better at showing fractures, bone erosion and acute intracranial hemorrhage. Acute hematomas are denser than brain and hence appear white.

Ultra-fast scanning – Sequences which allow images to be produced in less than 1 second can be used to perform dynamic scanning which can be used to monitor bolus injections of gadolinium so that cerebral blood volumes and regional blood-flow maps can be produced. This may be useful when investigating acute stroke.

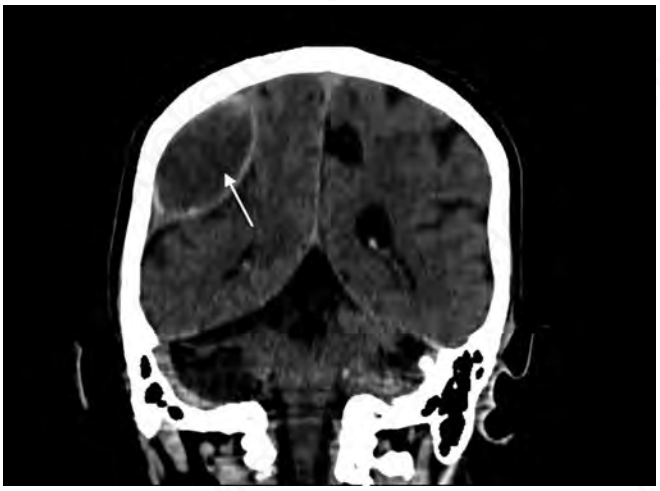


Fig. 1: CT scan coronal view showing extradural haematoma

Spine – CT scan is appropriate where the lesion can be localised to a particular area, e.g. lumbar disc disease.

Advantages

- CT is safer after recent trauma and in very ill patients
- More sensitive to intracranial calcification than MRI and better at showing fractures, bone erosion and acute intracranial hemorrhage (particularly subarachnoid hemorrhage)
- Acute hematomas are denser and hence appear white.

MRI

MRI is now the modality of choice for investigating most neurological diseases. Different tissues contain different amounts of hydrogen in various molecular environments; the appearance of the image depends principally on the concentration and molecular environment of the perturbed hydrogen protons and the applied radio frequency pulse.

The appearance can be changed by manipulating the radiofrequency pulse, using electronic protocols (sequences). The parameters measured are termed 'T_1' and 'T_2' relaxation times.

Images relying principally on contrast produced by T_1 relaxation are termed 'T_1-weighted' (T_1W) and show CSF darker than brain. They show gross anatomical detail of the brain and spinal cord. T_1W imaging is more sensitive to subacute hemorrhage and fat-containing structures.

Water (and therefore CSF) appear white on T_2-weighted (T_2W) images which are very sensitive to increase in cerebral water (as in most inflammatory and neoplastic diseases of CNS). T_2W images are more sensitive than T_1W images to edema, demyelination, infarction and chronic haemorrhage.

Hydrogen protons in bone or in areas of calcification return little signal and therefore appear dark on both T_1W and T_2W sequences.

After hemorrhage, haemoglobin liberated from RBCs degrades to methaemoglobin and then hemosiderin.

Methaemoglobin in subacute hematoma returns high signal on T_1W sequences. Hemosiderin in chronic hematoma returns low signal on both T_1W and T_2W sequences and therefore appears similar to bone.

Fluid attenuated inversion recovery (Flair) is a useful pulse sequence that produces T_2W images in which the normally high signal intensity of CSF is suppressed. Flair images are more sensitive than standard spin echo images for any water-containing lesions or edema.

Differential Diagnosis on MRI

Differential diagnosis on MRI is given in Table 2.

Table 2: Differential diagnosis on MRI

• Multifocal white matter (high-signal) lesions on T_1 weighted sequences:
– Posterior reversible encephalopathy syndrome (PRES) – Accelerated hypertension, pregnancy (toxaemia), acute GN, cyclosporine HUS, TTP
– Multiple sclerosis
– Infection – progressive multifocal leucoencephalopathy, Lyme disease, opportunistic infections
– Inflammatory – acute disseminated encephalomyelitis, sarcoidosis
– Cerebrovascular disease – migraine, toxaemia of pregnancy, subacute atherosclerotic encephalomyelitis
– Vasculitis – granulomatous, systemic necrotizing, rheumatoid
– Neoplasm – metastasis
– Toxic – pontine myelinolysis, post-radiation change
• Materials returning high-signal on T_1 weighted sequences:
– Fat (including fat-containing tumour products)
– Subacute hematoma (methaemoglobin) (Fig. 2)
– Melanoma (melanin is paramagnetic)
– Flowing blood (on some sequences)
– Paramagnetic contrast agents (e.g. gadolinium)
– White matter
– Manganese in acquired liver disease and total parenteral nutrition
– Metastasis from melanoma
– Wilson disease (in globus pallidus), copper overload (Fig. 3)
– Lesions in areas containing fat (e.g. the orbit for optic neuritis)
– Functional MRI - Blood oxygen level dependent (BOLD)

Fat suppression sequences – Fat appears bright on standard T_1W and T_2W sequences. Sequences that suppress the fat signal are used to investigate suspected fat-containing tumors and lesions in areas containing fat (e.g. the orbit).

Other Magnetic Resonance Techniques

- Magnetic resonance spectroscopy – can be used to measure cerebral metabolites. It has been used in some clinical situations (e.g. to distinguish radionecrosis from recurrent neoplasms) and to assay cerebral levels of drugs.

Clinical MRI - The patient is given specific tasks to perform (motor, language, visual, etc.) while MRI sequences are being performed. These EPI sequences are able to detect increased O_2 delivery and blood flow to areas of the brain that are responsible for these, which are shown in colour on the MRI images.

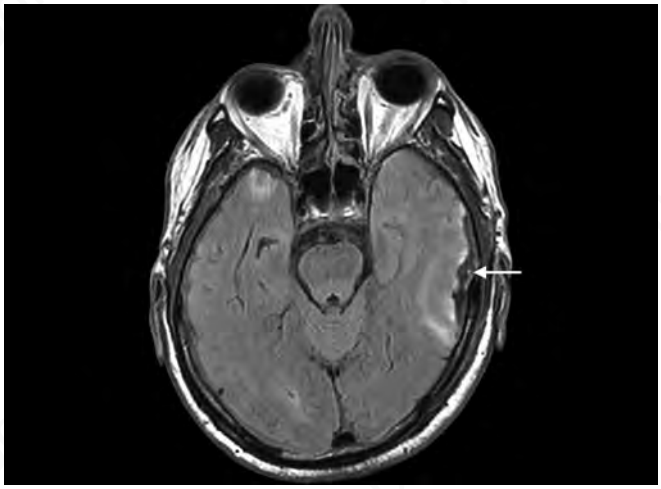


Fig. 2: MRI T2 flair image axial view showing subdural haematoma

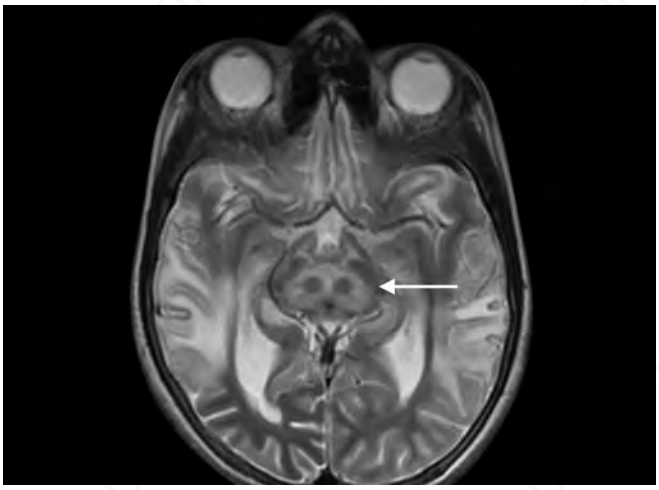


Fig. 3: MRI in Wilson's disease-panda sign

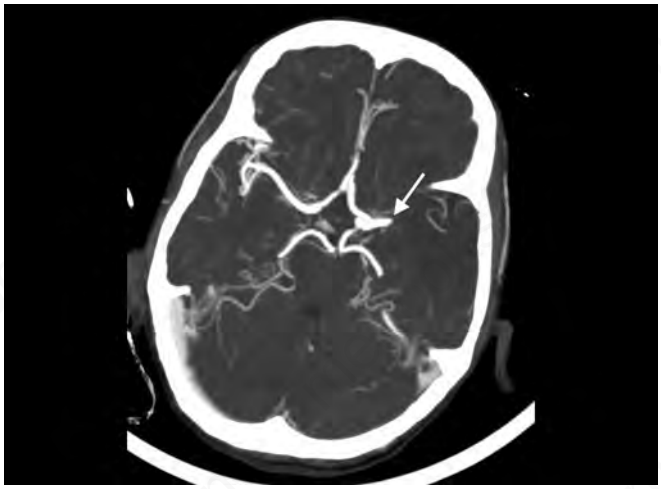


Fig. 4: CT angio MIP image - (maximum in ten sity projection) in MCA infarct showing occlusion beyond M2

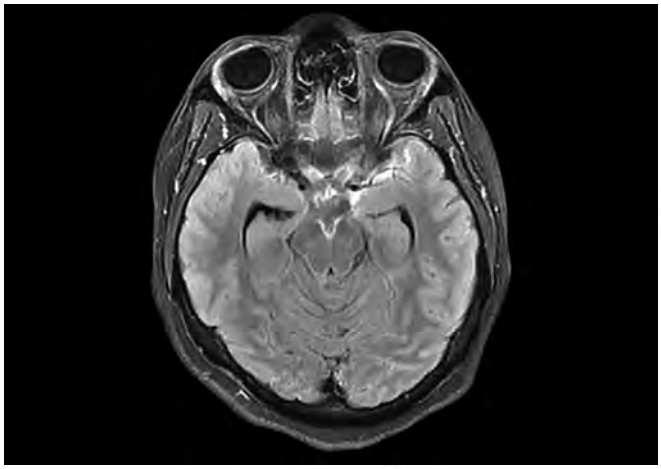


Fig. 5: MRI axial view postcontrast flair images in meningitis

High resolution MRI - Use of high resolution sequences allows appreciation of cyst and scolex appearance in neurocysticercosis.

MR angiography (MRA) – Because moving hydrogen atoms in flowing blood return different signals from those in static tissue, sequences are designed to demonstrate vessels (Fig. 4). Two sequences are in clinical use – 'time of-flight' and phase-contrast. Both rely on post-processing of images by the scan computer to produce the angiogram. They can selectively demonstrate arteries or veins, based on the velocities and direction of blood flow, and can be used to demonstrate patency of blood vessels. No injection contrast is needed, but MRA can be performed after injection of gadolinium to show vascular distortions caused by intracranial mass lesions or AV malformation.

Contrast enhancement – Following i.v. injection of a paramagnetic agent (e.g. gadolinium), areas of blood-brain barrier breakdown are enhanced. Contrast agents are used for detection, preoperative assessment and follow-up imaging of intracranial tumours, inflammatory disease (especially meningeal) (Fig. 5) and in patients presenting with cranial nerve palsies.

MRI sequences – CSF signal suppressing sequences – Lesions in the paraventricular brain (e.g. multiple sclerosis) may be difficult to detect because of high signal returned by the adjacent CSF. Special sequences can be used (e.g. Flair), which produces a scan with dark CSF that increases the conspicuousness of periventricular plaques.

MRV – In suspected CVT. Contrast MRV to differentiate between slow flow and occlusion.

ANGIOGRAPHY

Cerebral angiography is usually performed by selective catheterization of the carotid or vertebral arteries.

Passage of the contrast bolus through the cranium from artery to vein is recorded by a series of radiographic exposures timed to show maximum opacification of each component of the vascular tree. Subtraction of each digitized image from a baseline image (obtained before the arrival of intravascular contrast) is performed electronically. This process removes details of the baseline image (bone) from subsequent images, so they show only the opacified vessels.

Digital Subtraction Angiography

Because digitized systems are sensitive to lower concentrations of contrast medium, images can be obtained following both intravenous (IV-DSA) and intra-arterial (IA-DSA) injection. IV-DSA has the advantage of a lower risk of complications of causing stroke. MRI can provide images of a quality similar to those obtained by IV-DSA without exposing patients to the risk of ionizing radiation and radiographic contrast agents. Thus IA-DSA is reserved for specific situations in which very high-resolution imaging is required (e.g. suspected intracranial aneurysm).

Although the role of cerebral angiography is declining, its use in therapy is increasing as endovascular therapies for treatment of brain AV malformations and aneurysms become more widely available.

Uses

1. To demonstrate source of subarachnoid or other intracranial hemorrhage. Multiple views are necessary to demonstrate configuration of an aneurysm prior to surgical intervention, and detailed angiography is performed to demonstrate vessels feeding and draining an angiomatous malformation.
2. To demonstrate displacements and vascularity due to an intracranial tumour.
3. To demonstrate vessel occlusion, stenosis or plaque formation.
4. To identify A-V malformation.

RADIONUCLIDE SCANNING

Metabolism and blood flow can be evaluated using the techniques of positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Both techniques measure cerebral blood flow, but PET provides unique information about cerebral metabolism of oxygen and glucose using oxygen-15 and fluorine-18 respectively. Interictal PET localize the lesion in focal epilepsy.

$^{99M}T_C$ HMPOA is used in SPECT. This is lipophilic and crosses the intact blood-brain barrier to bind to unspecified receptors. Its distribution reflects cerebral blood flow and remains stable for about 1 hour, during which scanning is performed.

Uses – Investigation of patients with seizure disorders, dementia, neoplasms and ischemic disease. Both are used to complement and validate MRI data. Ictal SPECT to localize seizure onset zone in focal epilepsy.

ULTRASONOGRAPHY

Ultrasonography is useful in CNS only when performed through a bone defect (e.g. an open fontanelle or after laminectomy). Duplex ultrasound combines high resolution real-time imaging with Doppler flow analysis and is used to evaluate the cervical carotid arteries. *Uses* – To evaluate hydrocephalus and neonatal hemorrhage in young children. Duplex scanning has replaced angiography for screening patients with suspected carotid bifurcation stenosis.

CLINICAL NEUROPHYSIOLOGY

The ability to generate and propagate electrical potentials is a fundamental property of nerve and muscle cells. For the recording of such activity and the information it can provide about brain and neuromuscular disorders, three techniques are used –

Electroencephalography

EEG is the study of the electrical activity of the brain as detected by 8-16 pairs of electrodes attached to the scalp in standard positions. The wave forms are classified according to their frequency – delta <4 Hz (Stage III and IV sleep). Theta 4 to 8 Hz (drowsiness), Alpha 8 to <13 Hz (relaxed wakefulness in posterior region), Beta >13 Hz (frontocentral region).

(a) ***The probability of detecting epileptiform*** activity increases with repeated EEG records in 90% of patients with epilepsy. An epileptiform activity will be detected after four 20 minutes routine EEG records.

(b) ***Detection of ictal discharges during a clinical attack*** – Ictal discharges usually comprise of focal or lateralized rhythmic delta-theta or alpha-beta activity in

focal seizures (Temporal, occipital, parietal or frontal). Generalized spike and wave activity and fast activity is seen in generalized seizures, (absence, myoclonic, tonic-clonic seizures). In photosensitive epilepsies like juvenile myoclonic epilepsy (JME), photic stimulation evokes epileptiform discharges (photoparoxysmal response).

(c) ***Presurgical evaluation*** – Special intracranial electrodes are placed over the cortex (subdural grid, or in the brain parenchyma (depth electrodes) close to the suspected epileptic focus. Ictal discharges are then studied during prolonged video EEG monitoring to localize the seizure onset zone as part of presurgical evaluation of epilepsy. The epileptogenic zone is then resected as a surgical treatment for refractory epilepsy.

In herpes encephalitis periodic lateralized epileptiform discharges (PLEDs) are seen.

Periodic patterns on EEG – (a) Periodic Sharp Wave Complexes (PSWC) of frequency 0.5 to 2 Hz in Prion diseases, e.g. Creutzfeldt-Jakob disease. (b) Triphasic waves in hepatic encephalopathy but may be seen in other metabolic encephalopathies like uraemia. (c) Periodic complexes of subacute sclerosing encephalitis consist of sharp and slow waves accompanied by myoclonus occurring at interval of 5–15 secs. (d) Generalized periodic pattern is seen in coma due to severe brain injury caused by hypoxia, cardio-respiratory arrest and suggests a poor prognosis.

Uses

Epilepsy

(a) *Detection of epileptiform activity between seizures* (interictal epileptiform discharges, IEDs) supports a clinical diagnosis of epilepsy. IEDs include localized (non-physiological) or generalized spike or sharp waves, with or without slow waves, occurring singly or in bursts and not accompanied by any clinical changes.

(b) *Detection of ictal discharges during a clinical attack* – confirms that the attack is of epileptic origin. Ictal discharges usually comprise bursts of sharp or spike and slow waves, or rhythmic activity at various frequencies. In absence epilepsy, overbreathing commonly evokes absence attacks accompanied by typical generalized 3 Hz spike and slow wave discharges. In photosensitivity, photic stimulation evokes epileptiform discharges.

(c) *Classification of epilepsy* – Focal IEDs or generalized IEDs starting focally are consistent with partial epilepsy; generalized symmetrical IEDs are associated with generalized epilepsies.

(d) *Underlying cause* – Focal delta activity suggests a localized structural lesion while diffuse encephalopathies (toxic, metabolic, degenerative) produce generalized slow waves.

(e) *Assessment of treatment in epilepsy* – In status epilepticus and childhood absence epilepsy, improvement in clinical attacks correlates closely with a reduction in discharges. Persistence of generalized IEDs increases the risk of seizure recurrence in children.

(f) *Presurgical evaluation* – Special intracranial electrodes are placed close to the temporal lobes extra- or intracerebrally and ictal discharges studied during prolonged monitoring to localize the epileptogenic zone before surgical resection.

Encephalitis and other encephalopathies

- In encephalitis EEG shows a diffuse, slow wave abnormality which, if associated with periodic sharp wave discharges in the temporal region, is strongly suggestive of herpes simplex encephalitis.
- Short-interval (0.5-4 seconds) periodic discharges or triphasic waves in Creutzfeldt-Jakob disease and metabolic encephalopathies.
- Long interval (> 4 seconds) periodic discharges in subacute sclerosing panencephalitis.

Evoked Potentials

The electrical responses of CNS structures to sensory input are usually indiscernible against the background of an ongoing EEG, or over the spinal cord. However, electronic averaging of the small responses to discrete repeated stimuli enables identification of these so-called evoked potentials. The modalities are:

(a) Visual evoked potentials (VEPs) – are averaged potentials evoked by visual stimuli and detected by scalp electrodes placed over the occiput. In multiple sclerosis, VEPs demonstrate abnormality when MRI is normal, because the optic nerves are involved early; however a similar response pattern may occur in patients with ischemic or compressive lesions. (i) In multiple sclerosis there is delayed p100 response. (ii) In spondylotic myelopathy there is delayed central conduction at the level of cervical spinal cord. (iii) Denervating disorders – Spontaneous potentials like positive sharp waves and fibrillations are due to active denervation. The MUAPs in denervating disorders like anterior horn cell diseases are large (amplitude), wide (long duration) and due to expansion of motor unit (reinnervation). (iv) Primary myopathy – The MUAPs are small in amplitude and polyphasic due to breakdown of muscular fibre and small size of motor

unit. This is typically seen in muscular dystrophies (LGMD, DMD, BMD).

(b) Brainstem auditory evoked potentials (BSAEPs) – (a) To determine deafness in neonates and very young children. (b) Suspected acoustic neuroma. (c) Comatose patient. (d) Multiple sclerosis.

(c) Somatosensory evoked potentials (SEPs) – (a) Distinguish between peripheral, spinal cord and central lesions. (b) For identifying brachial plexus lesions (since peripheral nerve conduction measurements are inappropriate).

Electromyography and Nerve Conduction Studies

Electromyography (EMG)

Electromyography is performed using a needle electrode which records the electrical potential generated by about ten muscle fibres in the vicinity of the needle tip. In normal muscle, no electrical activity occurs with the muscle at rest. During slight voluntary contraction, a few motor axons discharge at rates of about 10–20/second, each axon activating the muscle fibres it innervates. The summated electrical response from the muscle fibres is referred to as the motor unit action potential (MUAP).

Denervating disorders – In conditions causing degeneration of motor neurons (e.g. axonal peripheral neuropathy, motor neuron disease), muscle fibres losing their nerve supply depolarize spontaneously. The resulting small potentials recorded from muscles at rest are termed 'fibrillations' and 'positive sharp waves'. Fibrillation potentials become less prominent during re-innervation. In motor neuron disease, neuromyotonia and radiation nerve damage, spontaneous discharges of motor units produce fasciculation potentials in resting muscles. These are similar to MUAPs in appearance.

Primary myopathy – Shrinkage of muscle fibres in muscle disease if uniform, MUAPs have normal outlines but are smaller in number, if non-uniform, MUAPs become small but more complex. The number of motor neurons is usually normal, so a maximum contraction, though weak, produces a full interference pattern. The picture is seen in most metabolic myopathies and in some muscular dystrophies. In Duchenne and Becker muscular dystrophies and acquired inflammatory myopathy, muscle fibres necrosis probably causes disconnection of part of muscle fibres from their nerve supply. This functional denervation produces fibrillation potentials, and collateral reinnervation with compensatory muscle hypertrophy gives rise to long-duration, unstable polyphasic MUAPs, which may have high altitude components. In myotonic dystrophies, needle insertion provokes bursts of muscle action potentials of diminishing frequency and amplitude, giving rise to a characteristic dive bomber sound when modified through a loudspeaker.

Radiculopathy – In severe cases the finding of retained sensory action potentials in an anaesthetic area indicates a lesion proximal to the dorsal root ganglia.

Quantitative EMG – Using a computer, the interference pattern can be decomposed into constituent MUAPs, allowing parameters such as duration, amplitude and polyphasicity to be quantified.

Nerve Conduction Studies

Measures conduction in response to electrical stimulus.

Distal latency, i.e. latency from stimulus to recording electrodes, amplitude of the response and conduction velocity provide information of motor and sensory nerve function, i.e. measurement of conduction distance allows calculation of the maximal motor or sensory conduction velocities. These are normally in the range of 50–60 m/second in the arm and 40–50 m/second in the leg. The most easily studied nerves are the median, ulnar and radial nerves in the arm, and common peroneal, tibial and sural nerves in the leg.

(a) *Peripheral neuropathy* – Electrophysiology (EMS and NCS) differentiates between demyelinating and axonal neuropathies and narrows the differential diagnosis of peripheral neuropathies.

(b) *Radiculopathy* – A normal sensory nerve action potential (SNAP) in presence of impaired sensation indicates a lesion proximal to dorsal root ganglia like in radiculopathy.

(c) *Demyelinating neuropathies* – Delayed distal latencies, prolonged conduction velocity, conduction block, delayed F wave (a late response recorded from muscle as a result of propagation of nerve impulse to motor neuron cell and back again) in case of proximal demyelination (GBS).

(d) *Axonal neuropathies* – There is reduction in number of nerve fibres in a nerve. There is reduction in amplitude or absent CMAPs (compound muscle action potential) and SNAPs. The conduction velocity, latency is normal. Denervating potentials are seen on needle EMG.

(e) *Entrapment neuropathy* – Disorders such as carpal tunnel syndrome, neuropathy at the elbow and peroneal palsy at the knee cause selective demyelination with focal slowing of conduction velocity or block, which is used to localize the lesion. The degree of conduction abnormality may indicate the severity and longevity of the nerve lesion.

Table 3: Indications for nerve conduction studies and electromyography

Clinical presentation	*Differential diagnosis*	*Neurophysiological findings*
Localized weakness and sensory symptoms	Peripheral nerve lesion	Nerve conduction and EMG changes limited to distribution of one nerve.
	Radiculopathy	Sensory nerve potential retained in area of numbness. EMG changes, confined to one myotome
Generalized weakness and sensory symptoms	Peripheral neuropathy	Slow motor and sensory conduction velocities in demyelinating neuropathy. Reduced response amplitudes and EMG signs of denervation in axonal neuropathy Combination of the above common
	Polyradiculopathy and sp. cord lesions	Normal motor and sensory conduction
Weakness without sensory symptoms	Motor neuron disease	Retained sensory nerve conduction, widespread fasciculation potentials and EMG signs of denervation/ re-innervation
	Motor neuropathies	Slowing of motor conduction velocity; may have conduction block, retained sensory responses
	Neuromuscular transmission disorders	Myasthenia gravis – may exhibit muscle action potential decrement on repetitive nerve stimulation, abnormal 'jitter' or single-fibre EMG Lambert-Eaton myasthenic syn. – low resting compound muscle action potential amplitude, increasing after maximal voluntary activation or tetanic nerve stimulation
	Primary myopathy	Usually normal nerve conduction; EMG may show fibrillation potentials caused by muscle fibre necrosis, myotonia, low-amplitude polyphasic motor action potentials, full 'interference pattern' of electrical activity despite weak contraction

(f) *Myasthenic disorders* – In *myasthenia gravis* there is decremental response on RNS (repetitive nerve stimulation) on slow frequency. In Lambert Eaton syndrome there is incremental response on high frequency RNS.

Indications for nerve conduction studies and electromyography.

See Table 3 for the Indications for nerve conduction studies and electromyography and findings in the studies.

Immunochemistry studies for muscular dystrophies like Duchenne, Becker, limb girdle muscular dystrophies (e.g. sarcoglycanopathies). Congenital muscular dystrophies, congenital myopathies (central core, nemaline).

MUSCLE BIOPSY

Diagnostic value of muscle and nerve biopsy is given in Tables 4 and 5.

Table 4: Diagnostic value of muscle biopsy

1. Polymyositis/dermatomyositis.
2. Myotonic dystrophy.
3. Metabolic muscle disease, e.g. glycogen storage disease.
4. Trichinosis, toxoplasmosis.
5. Polyarteritis.

Table 5: Diagnostic value of nerve biopsy

1. Differentiating between axonal and demyelinating neuropathies (of prognostic significance).
2. Demonstrating infiltration of peripheral nerves, e.g. amyloidosis, sarcoidosis, leprosy, carcinoma, vasculitis.
3. Diagnosis of congenital hypertrophic neuropathies.
4. Giant axonal neuropathy.

LUMBAR PUNCTURE AND CSF EXAMINATION

Lumbar puncture (LP) allows access to CSF. The volume of CSF is about 150 mL produced at a rate of 300–500 ml/day.

Functions of CSF:

- Provide a protective cushioning effect for the brain and sp. cord
- Preserves a stable chemical environment
- Removes waste products of cerebral metabolism

Indications for LP

1. ***Diagnostic:***
   (a) *Infection* – Bacterial meningitis. Changes in CSF in non-bacterial meningitis and encephalitis are often nonspecific and more detailed testing may be required.
   (b) *Subarachnoid hemorrhage* – LP should be performed only in those cases of SAH that are negative on CT scan, and ideally should be delayed for 6 hrs after onset of hemorrhage to allow blood to reach lumbar region. Xanthochromia, a yellow discoloration caused by pigments released from degenerated RBCs, is found after 24 hours and may last up to 7 days.
   (c) *Inflammatory disorders* – Inflammatory neuropathies (including Guillain-Barre syndrome), SLE, sarcoidosis and Behcet's syndrome with neurological involvement may all result in nonspecific CSF abnormalities.
   (d) *Demyelination* – Analysis of paired CSF and serum for oligoclonal IgG forms part of laboratory supportive criteria for multiple sclerosis, but local synthesis of IgG also occurs in inflammatory and infectious disorders.
   (e) *Malignant disease and other disorders* – Neurological symptoms arising from carcinomatosis, lymphoma, leukaemia, paraneoplastic disorders, hepatic encephalopathy and septic cerebral emboli may be an indication for CSF analysis.
2. ***Therapeutic:***
   – *Drug instillation* – Cytotoxic drugs for lymphoma or leukaemia treatment may require intrathecal administration. Also antibiotics and antifungal agents, pump systems are used to deliver intrathecal baclofen for resistant spinal spasticity, and also to administer analgesia for post-operative pain relief.
   – *Reducing volume* – Benign intracranial hypertension may require repeated removal of large volumes of CSF to reduce CSF pressure rapidly.

Contraindications

1. *Raised CSF pressure* – Symptoms suggestive of raised pressure, focal neurological signs and a fluctuating conscious level all require a CT scan before LP because of risk of herniation of brain substance through foramen magnum.
2. *Spinal block* – LP may precipitate a sudden deterioration if there is a spinal block.
3. *Coagulopathies* – because of increased risk of epidural hemorrhage. Value of information gained from the procedure must be weighed against the risk, and replacement therapy must be available.
4. *Local suppuration* – Infection can be introduced into CSF and subsequently meningitis, if there is skin infection at lumbar puncture site.

Technique

1. *Position* – The patient is placed on his side at the edge of the bed with the knees drawn up and the head bent forward to get maximum flexion of the spine. 2. *Site* – The skin and fascia over the lumbar space selected are sterilised (usually between the spines of the 3rd and 4th lumbar vertebrae), this space being a plane passing through the highest points of both iliac crests) and infiltrated with a small amount of 1% lignocaine. 3. *Puncture* – The lumbar puncture needle is inserted through the anaesthetised skin in the mid-line and passed forwards and slightly upward till it reaches the tough spinous ligament. This is pierced. A sudden "give" or cessation of resistance indicates that the needle has passed through the dura and entered the intrathecal space. The stylus is then removed and the fluid should flow out at once. It should be withdrawn slowly, if the tension is high.

Difficulties that may be encountered

- *CSF does not flow* – The position of the needle should be adjusted slightly or the stylet re-inserted to dislodge anything that may have blocked the lumen.
- *Blood stained fluid* – may be due to subarachnoid hemorrhage or puncture of a vessel. To differentiate 2-3 mL CSF should be collected in 3 bottles. In SAH, fluid will be uniformly stained, in traumatic tap CSF clears in the third bottle.
- *Dry-tap* – usually results from poor technique, but may be caused by anatomical anomalies, previous surgery, or infections causing arachnoiditis.

Complications of Lumbar Puncture

1. *Headache* – is probably caused by subsequent leakage of CSF through the dural hole. Risk of headache may be reduced if patient sits up for a few hours after the procedure. Dural leakage can be minimized using a fine spinal needle, with its bevel in the spinal axis.
2. *Herniation of the brain or spinal cord* – can be avoided by excluding intracranial lesions before and undertaking LP. If consciousness deteriorates or respiration fails, immediate surgical decompression is required. Meanwhile the raised intracranial pressure should be reduced by 20% mannitol, 1 g/kg body weight by rapid iv infusion.

3. *Other complications*
   - Meningitis or epidural abscess, caused by poor asepsis
   - Intracranial bleeding, spinal or intracerebral subdural hematomas
   - Damage or infection of the intervertebral disc
   - Intraspinal dermoid cyst

Components of Normal CSF

Components of normal CSF are given in Table 6.

Physical Characters

1. Pressure – Normal in horizontal position 50-180 mm. of water; in sitting position 200–250 mm. Increased tension – intracranial tumour or haemorrhage or intracranial sinus thrombosis, meningitis, meningism, hydrocephalus, benign intracranial hypertension, uraemia and fulminant hepatic failure and sometimes encephalitis. Decreased tension – subdural hematoma, spinal subarachnoid block or block in region of foramen magnum, repeated lumbar punctures. CSF leak causing intracranial hypotension.
2. Appearance –
   (a) *Normal* – Clear and colourless.
   (b) *Turbid* – in meningitis. Fibrin clot "cobweb" usually in tuberculous meningitis. A pellicle may also develop in other forms of meningitis, poliomyelitis, intraspinal tumour, general paresis and epidemic encephalitis.
   (c) *Blood-stained* – Intracerebral haemorrhage, subarachnoid haemorrhage, leakage of blood from cerebral tumour, haemorrhagic form of encephalitis, trauma of spinal cord, trauma of needle, haemorrhagic diathesis (including anti-coagulants, bleeding from angioma or from A-V malformation).
   (d) *Xanthochromia* (yellow tinting) – (i) Recent subarachnoid bleeding. (ii) Spinal block. (iii) Guillain-Barre syndrome. (iv) Acoustic neuroma. (v) Subdural haematoma. (vi) Purulent meningitis. (vii) Rifampicin.

Differentiating features between traumatic tap and subarachnoid haemorrhage are given in Table 7.

CSF in Meningitis

CSF findings in different causes of meningitis are given in Table 8.

Chemical Composition

1. Protein – Normal <0.45 g/litre. *Increased* – in purulent meningitis, encephalitis, poliomyelitis, multiple sclerosis and neurosyphilis, spinal cord compression;

Table 6: Components of normal CSF

• pH 7.3	
• Osmolality 295 mOsmol/L	
• Total protein	0.1–0.45 g/L
– Pre-albumin	2–8%
– Albumin	45–75%
– γ-globulin	1–10%
• Glucose	2.22–3.89 mmol/L
• Cells	1–4 × 10^5/ l
• Sodium	135–148 mmol/L
• Potassium	2.5–3.3 mmol/L
• Chloride	116–128 mmol/L
• Bicarbonate	23–30 mmol/L
• Lactate	1.1–1.9 mmol/L

Table 7: Differentiating features between traumatic tap and subarachnoid haemorrhage

	Traumatic tap	*Subarachnoid haemorrhage*
Xanthochromia	Absent	Present after centrifugation
Clotting	May occur	Absent
Blood staining	Varies from tube to tube	Usually uniform in all tubes
Pressure	Usually normal	Elevated
Repeat puncture at higher interspace	Often clear	Similar to initial tap

Table 8: CSF findings in different cuses of meningitis

Type	*Appearance*	*Cells (µl)*	*Protein (g/L)*	*Blood glucose (mmol/L)*
Bacterial	Purulent	>1000 (>60% neutro)	>0.8	>50% level, may be absent
Tuberculous	Viscous, may clot on standing	5–400 (>80% lympho)	0.8–4	>50% level, may be absent
Viral	Clear or cloudy	10–1000 (>80% lympho)	<0.6	>50% level, may be low in measles
Fungal	Clear or cloudy	<400, mixed inflammatory cells	<1.2	<50% level
Malignant	Clear or cloudy	<200 mixed inflammatory and malignant cells	<1.5	<50% level

intracranial tumour and cerebral arteriosclerosis. Also amyloidosis, alcoholism, diabetes, acoustic neuroma, cerebral toxoplasmosis.

Increase of cells and protein without alteration of sugar and chloride values – Virus encephalitis, brain abscess, subarachnoid haemorrhage, tumour, lead poisoning, aseptic meningeal reaction as in sinus thrombosis, lymphocytic choriomeningitis.

Protein-albumin cytological dissociation in GBS (elevated protein with normal cells).

Immunoglobulin (IgG) – Normal 0.5–4.5 mg/litre. Rises in demyelination and with neurosyphilis, primary lateral sclerosis, viral encephalitis, fungal meningitis, myelopathy due to vitamin B_{12} deficiency and subacute sclerosing encephalitis.

2. Chlorides – Diminished in purulent meningitis, and meningism, marked reduction in tuberculous meningitis. Also systemic disorders accompanied by hypochloraemia.
3. Glucose – *Reduced* – or absent in pyogenic meningitis, moderately decreased in tuberculous meningitis, in some viral meningitis like mumps, LCMV, measles. *Raised* – slightly in encephalitis, diabetes mellitus, carcinomatosis of meninges. *Normal* – in aseptic meningeal reaction, syphilitic meningitis.
4. Acetone – normally absent, its presence is of grave significance.

Cytological

Cell count – Normal 0–5 cells, lymphocytes. Between 10 and 100 per c.mm. – neurosyphilis, encephalitis, poliomyelitis, epilepsy, uraemia. 100 to 500 – tuberculous or syphilitic or aseptic meningitis, lymphocytic choriomeningitis and poliomyelitis. Over 500 – purulent meningitis.

Lymphocytosis – (a) Meningitis – Tuberculous, viral, spirochaetal, protozoal, rickettsial, carcinomatous, brucellar, chemical (e.g. after myelography), partially treated bacterial. (b) Parameningeal infections. (c) Poliomyelitis, herpes zoster. (d) Encephalitis. (e) Cerebral abscess. (f) Cerebral tumour. (g) Sinus thrombosis. (h) Following cerebrovascular accidents and subarachnoid haemorrhage. (i) Multiple sclerosis. (j) Post-traumatic. (k) Lead poisoning.

Polymorphonuclear leucocytosis – Pyogenic or fungal meningitis, acute syphilitic meningitis, early stage of poliomyelitis.

Mixed – Cerebral abscess, early stage of poliomyelitis, syphilitic meningitis, infection of bones of skull in neighbourhood of meninges and many cases of tuberculous meningitis.

Eosinophils – Pathognomonic of cerebral or spinal cysticercosis, primary amoebic meningoencephalitis, gnathostomiasis.

Plasma cells – in neurosyphilis, also peculiar large iron-containing cells (Hortega cells).

Malignant cells – in malignant growth of brain or spinal cord leukemic meningeal metastasis, primary CNS lymphoma, angiocentric lymphoma.

Bacteria and Parasites

1. Pyogenic organisms on smear and culture in purulent meningitis.
2. Tubercle bacilli in TB meningitis.
3. Leptospira in meningeal type of Leptospira icterohaemorrhagica infection.
4. Flagellated trypanosomes in sleeping sickness more easily seen in CSF than in blood.
5. Trichinella larvae in cerebral type of trichinosis.
6. Echinococci, cysticerci, yeasts (torula), fungi and actinomycotic granules in infection of the nervous system with these organisms.
7. Free living, motile amoebas in primary amoebic meningoencephalitis.

Serological

CSF is abnormal in most untreated patients of neurosyphilis with positive VDRL, FTA and TPHA tests.

2. DISORDERS OF SPEECH

Common terminologies in speech disorders are given in Table 9.

APHASIA

Control of speech in the cerebral cortex – Many sensory and motor activities are concerned in the four major language modalities – speech production, speech comprehension, reading and writing. The formulation of language is primarily a sensory function and demands the integration of auditory, visual and sensory events. It takes place in the cerebral hemisphere where predominant hand area (handedness) is situated and is called the dominant hemisphere. The left cerebral hemisphere is responsible for language function in more than 90% of normal right handed individuals and about 70% of normal left-handers.

Table 9: Common speech disorders	
Aphasia or dysphasia	A disorder of language with impaired comprehension and/or expression of spoken and/or written language.
Alexia	Inability to read. Other language functions like comprehension and expression being normal.
Agraphia	Inability to write. Other language functions are normal in pure agraphia.
Alexia with agraphia	Inability to read and write.
Alexia without agraphia	Inability to read, but writing is normal.
Dysarthria	Disorder of articulation, normal language function in pure dysarthria.
Aphonia and dysphonia	Disorder of voice (sound) production. Articulation and language functions are normal.
Broca or motor aphasia	Speech is nonfluent and effortful. May be meaningful. Phonemic (similar sounding) paraphasias (penail for pencil, tan for fan). Repetition is impaired and reading comprehension may be impaired. Associated right hemiparesis common.
Wernicke or sensory aphasia	Speech is meaningless. Fluent and effortless. Semantic (similar meaning) paraphasias (pencil for pen). Repetition is impaired. Associated right hemianopia is common. Aetiology is usually an embolic stroke.
Global aphasia	Speech comprehension as well as expression is severely impaired. Associated right hemianopia common. Recovery is to a Broca's aphasia as comprehension improves.
Anomic (nominal) aphasia	Localization is anywhere in the dominant hemisphere.

1. *Broca's area* – Once language is formed, the formulated language must be transmitted anteriorly by means of subcortical association fibres to the cortical area of expression just anterior to the motor cortex.
2. *Receptive area* – Here the spoken word is understood and appropriate reply or action initiated. The temporal lobe receptive area lies close to the auditory cortex of transverse gyrus of temporal lobe, and the parietal lobe area within angular gyrus.
3. *Arcuate fasciculus* – is a link between receptive and expressive areas in order to integrate function.

CLINICAL ASSESSMENT OF DYSPHASIA

1. *History* – Patient's native language and handedness and educational status.
2. *Conversational testing* – Spontaneous speech: (a) Nonfluent aphasia: Here there is decreased output to 10 or less words per minute accompanied by increased effort in production of words, dysarthria, and short phrase length. The lesion is anterior to fissure of Rolando. (b) Fluent aphasia. Here the output of words may reach 200 words per minute. Effortless speech with no dysarthria, but accompanied by paraphasia. Paraphasia is a substitution within a language which may be literal (replacement of syllable), verbal (replacement of word), or substitution of a meaningless nonsense word (neologism). Patient with fluent aphasia is unaware of the substitutions.
3. *Repetition of spoken language* – Repetition is disproportionately poor in conduction dysphasia. In the uncommon transcortical dysphasias repetition is excellent despite other language defects.
4. *Naming* – Difficulty in naming is useful in establishing dysphasia, though it does not help to localise the lesion further as it occurs in varying degrees in all forms of dysphasia.
5. *Reading and writing* – Disturbances of reading (alexia) and writing (agraphia) are usually part of a more generalised aphasia. Alexia with agraphia is due to damage to left angular gyrus. Pure agraphia with little or no speech defect occurs with left parietal lesion. Co-existence of dysgraphia, dyscalculia, finger agnosia, and right-left disorientation indicates a lesion of left angular gyrus.

APHASIC SYNDROMES

Various aphasic syndromes are listed in Table 10.

Major Aphasic Syndromes

1. Broca or motor aphasia – results from damage to posterior part of inferior frontal gyrus. Speech is slow, laboured, poorly articulated and reduced to a few words (telegraphic). Comprehension is little impaired.
2. Wernicke or sensory aphasia – Posterior lesions of superior temporal gyrus. It differs from Broca's aphasia in that comprehension is severely impaired. Speech is effortless and fluent but with frequent paraphrasias (inappropriate words or words with inappropriate syllables) and neologisms (non-existent words). An embolus to the inferior division of the middle cerebral artery, to the posterior temporal or angular branches in particular.

Table 10: Aphasic syndromes

1. **Major aphasic syndromes**
   - Broca aphasia
   - Wernicke aphasia
   - Global aphasia
   - Anomic aphasia
2. **Minor or disconnected syndromes**
   - Conduction aphasia
   - Transcortical aphasias (motor and sensory)
   - Restricted and transient 'mini-Broca'
   - Modality specific aphasias:
     - Pure word blindness
     - Pure word deafness
     - Pure word mutism (aphemia)
     - Agraphia.

3. Global aphasia – is the commonest variety of aphasia and occurs with large peri-Sylvian lesions. The expressive disturbance characteristic of Broca's aphasia is combined with loss of comprehension of equal severity. Speech is non-fluent. This may persist after large cerebral infarcts. With less extensive lesions there may be some recovery towards one of the former categories; usually because comprehension improves.
4. Anomic (nominal) aphasia – The term denotes certain language disorders that result from lesions that interrupt association pathways. Here the main defect is in naming objects. There are also pauses in speech, groping for words, and substitution of another word, phrase or gesture to convey the meaning. Lesion is deep in the basal portion of posterior temporal lobe, in frontal lobe and in angular gyrus. It may be a manifestation of early Alzheimer's disease or of confusional states. It may also be the only residual abnormality after recovery from Wernicke, conduction or transcortical aphasia.

Disconnection (Dissociative) Language Syndromes

The term denotes certain language disorders resulting not from lesions of the cortical language areas themselves but presumably from lesions that interrupt association pathways.

Conduction aphasia – Patient comprehends spoken and written language with only minor mistakes, but is unable to repeat what is heard or read. Spontaneous speech is fluent but paraphasic. Common cause is infarction in the angular gyrus.

Transcortical aphasia – Due to ischemic damage in the region between major vascular territories (watershed), the motor-sensory language areas may be isolated from the surrounding cortex. In the *sensory type,* disorder of language is much like Wernicke aphasia except for preservation of repetition. In the *motor type,* patient spontaneously produces a few grunts and syllables, can faultlessly repeat phases or even sentences that are heard or read. The lesion is subcortical in frontal lobe, or partially recovered Broca aphasia.

Other modality-specific aphasias – (a) *Pure word mutism* (aphemia) – Patient loses capacity to speak, but is able to write and to understand spoken words. (b) *Pure word deafness* – Patient can hear but cannot understand spoken language. Expressive speech remains normal. The lesions in the dominant temporal lobe (Heschl gyri).

DYSARTHRIA

Peripheral neuromuscular control of speech – There are two essential processes for the conversion of the thought conceived in the cerebral cortex into the spoken word, by means of the voluntary musculature – (a) phonation or the production of sound and (b) articulation.

Types and Causes of Dysarthria

1. *Spastic* – due to bilateral pyramidal lesion – e.g. pseudobulbar palsy, motor neuron disease, upper brainstem tumours. Speech slurred, monotonous, high-pitched indistinct 'hot potato' speech, some disturbance of swallowing, jaw jerk exaggerated. Rarely with unilateral lesion especially in thalamus.
2. *Rigid (Parkinsonian)* – due to extrapyramidal lesion – (a) Speech slow, laboured, intermittent and jerky – monotonous or festinate speech, or it may be hesitant with sudden outpouring of rapid speech (explosive speech).
3. *Ataxic* – Two types – (a) Defect in articulation itself in the form of slurring of consonants. (b) Disorder of rhythm of speech, i.e. disturbance of normal co-ordination between speech and respiratory movements. Speech is slurred, drunken. The rhythm is irregular, at times explosive staccato or scanning. *Causes* – cerebellar diseases, hereditary ataxias, multiple sclerosis, anticonvulsant drug toxicity.
4. *Flaccid* – due to lower motor neuron lesions – (a) *Facial paralysis* – causes difficulty with labials resulting in slurred speech. (b) *Tongue paralysis* – Gutteral speech. (c) *Palatal paralysis* – Nasal speech.

5. *Choreic and myoclonic* – Speech is interrupted by abnormal movements.
6. *Myasthenic* – Early stage – speech slurred with nasal twang occurring only when patient has been speaking for long. Later – persistent dysarthria and aphonia.

With pure disorders of articulation, language functions are intact. The only exception occurs with a restricted left frontal lesion and 'mini-Broca' aphasia, with recovery from mutism, elements of both aphasia and dysarthria can be recognised.

3. THE CRANIAL NERVES

OLFACTORY NERVE

Affection of olfactory nerves causes anosmia. Table 11 lists various causes of anosmia.

Table 11: Causes of anosmia

1. Head injury (fracture of cribriform plate).
2. Viral infection.
3. Tumours (usually meningioma).
4. Drugs – Penicillamine.
5. Endocrinal – Addison's disease, thyrotoxicosis.
6. Aneurysm of circle of Willis.
7. Tabes.
8. Refsum's disease.
9. Increased intracranial pressure (rare).

OPTIC NERVE

Anatomy – The visual system is composed of peripheral reception in retina, central pathway and cortical centres (Fig. 6).

Visual field defects tend to fall into patterns of one quarter or one-half of visual fields. Blindness in one quarter of a field is called quadrantanopia (quadrants = 1/4, an = without, opic = vision). Blindness in one half of a field is called hemianopia. When corresponding quadrants or halves of the fields, e.g. the right halves are affected, the defect is termed homonymous, and described as right or left. Patterns of visual field loss and causes are enumerated in Table 12.

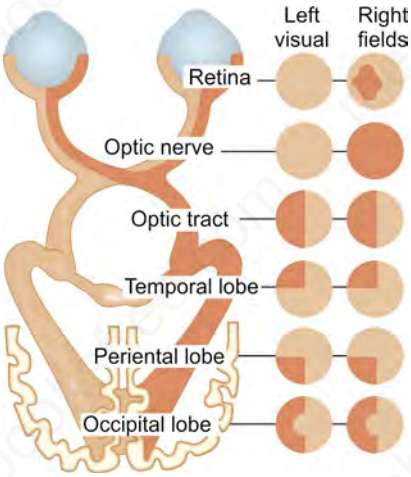


Fig. 6: Visual pathways showing various sites of interruptions and the field defects thus produced

III, IV AND VI. CRANIAL NERVES

Oculomotor – Paralysis causes – 1. Diplopia. 2. External paralytic squint (divergent squint). 3. Inability to move eye upwards, directly downwards or directly inwards. 4. Ptosis due to paralysis of levator palpebrae. 5. Pupil dilated and not reacting to light or accommodation.

Trochlear – 1. Diplopia on looking in direction of action of superior oblique, i.e. downwards and inwards. 2. Head inclined forwards and towards shoulder on sound side to avoid giddiness when looking downwards.

Abducent – 1. Diplopia on looking outwards. 2. Convergent squint. 3. Paralysis of external rectus with inability to turn the eye outwards beyond midpoint (Internal paralytic squint). 4. Head turned towards affected side.

Causes

1. *Within brainstem* (Nuclear and fascicular lesions) – Neoplasms, vascular lesions, encephalitis, syringobulbia, tuberculoma.
2. *At base of brain* – Meningeal affections: Tuberculous, bacterial and fungal meningitis, carcinomatous infiltration of meninges, meningovascular syphilis. Direct neoplastic invasion from sinuses and nasopharynx, Guillain-Barre syndrome, sarcoid and herpes zoster.
3. *Lesions at petrous tip* – Mastoiditis or otitis media may cause diffuse inflammation of petrous bone with combination of 6th, 7th and 8th nerve palsies.
4. *Lesions in region of cavernous sinus* – Cavernous sinus thrombosis (6th nerve most vulnerable), intrasellar tumours such as chromophobe adenomas (3rd nerve). Aneurysmal dilatation of intracavernous portion of carotid artery, carotid-cavernous fistula.

Table 12: Patterns of visual field loss and causes

Site of lesion	*Field defect*	*Causes*
Optic nerve	Monocular scotoma or blindness	MS, optic nerve glioma, ischemic optic neuropathy, compression by tumour, Leber hereditary optic atrophy
Optic nerve and chiasma	Heteronymous defect (field defects that differ in the two eyes)	Craniopharyngioma and other suprasellar tumours
Optic chiasma	Bitemporal hemianopia	Pituitary tumour, meningioma of tuberculum sellae, craniopharyngioma, aneurysm
Optic tract	Homonymous hemianopia	Tumour, rarely demyelinative
Lateral geniculate	Homonymous hemianopia	Post cerebral artery occlusion, tumour
Geniculocalcarine pathway	Homonymous hemianopia	Infarction, mass lesion, demyelinative
Superior temporal lobe	Inferior quadrantanopia or noncongruent homonymous hemianopia	Temporoparietal infarction, mass lesion
Occipital lobe and calcarine cortex	Homonymous hemianopia, congruent; central homonymous hemianopic scotoma, homonymous altitudinal hemianopia loss of vision in corresponding upper or lower visual fields, blindness with retained pupillary reflexes	Post cerebral artery occlusion, infarction of one occipital pole Infarction above or below calcarine sulcus Bilateral infarction; central scotoma, if only occipital lobes affected

5. *Lesions at superior orbital fissure and orbital apex* – Neoplasms such as meningiomas.
6. Tolosa Hunt syndrome – is idiopathic inflammatory granulomatosis of superior orbital fissure causing III, IV, VI and V nerve first division involvement. Clinically it is indistinguishable from anterior cavernous syndrome. Table 13 lists the causes of painful ophthalmoplegias.

Impaired vertical gaze

1. Parinaud's syndrome.
2. Richardson-Steele syndrome (Progressive supranuclear palsy)
3. Grave's disease.
4. Thalamic hemorrhage.

Isolated iv nerve palsy

Cerebral peduncle lesion.

Oculogyric crisis (Oculogyric spasm). Sudden paroxysmal, tonic, upward deviation of both eyeballs for seconds or minutes may be observed in post-encephalitic Parkinsonism, petit mal epilepsy, Millard Gubler syndrome or may be drug-induced, e.g. Phenothiazine.

Table 13: Painful ophthalmoplegic syndromes

A. III nerve palsy:
1. Diabetes mellitus, vasculitis.
2. Intracranial aneurysms – Posterior communicating artery, internal carotid artery.
3. Ophthalmoplegic migraine.
B. VI nerve palsy:
1. Tolosa-Hunt syndrome.
2. Gradenigo's syndrome.
3. Carcinoma of nasopharynx.
4. Internal carotid artery aneurysm (infraclinoid).
C. Total ophthalmoplegia:
Superior orbital fissure syndrome.

Nystagmus

Nystagmus is a rhythmic repetitive oscillation of the eyes. It is initiated by a slow eye movement that drives the eye off target followed by a fast (jerk nystagmus) or another slow (pendular nystagmus) corrective eye movement in the opposite direction. Some of the types and causes of nystagmus are listed in Table 14.

Causes

1. Ocular lesions.
2. Labyrinthine disease.
3. Brainstem and cerebellar disease.

Degrees of nystagmus – Nystagmus present with eyes deviated less than 30% from the midline is abnormal.

Table 14: Causes and types of nystagmus

Cause	*Type of nystagmus*
• Retinal or ocular	
• Congenital cataract	Rapid pendular
• Congenital macular defect	Increased on looking to the sides
Albinism	Present throughout life
Labyrinthine (Vestibular)	
(a) Physiological	Nystagmus in plane of rotation Horizontal nystagmus on caloric testing
(b) Pathological	Slow phase to side of lesion, quick phase to normal side
Damage to labyrinth or vestibular nerve, e.g. Meniere's disease	Turning eyes away from side of lesion increases amplitude but does not change direction of nystagmus
Vestibular neuronitis Ischemia	Vertigo Tinnitus and hearing loss often
CNS nystagmus	
Vascular disease. Demyelination Neoplasm. Wernicke's encephalopathy Drug toxicity, e.g. phenytoin	Horizontal, vertical, rotatory or dissociate Vertigo seldom. Signs of brainstem involvement

1st degree – Nystagmus with eyes deviated to one side.

2nd degree – Nystagmus with eyes deviated to one side and in midline position also.

3rd degree – Nystagmus in all directions of gaze.

Types of Nystagmus

1. Optokinetic nystagmus (OKN) – Impaired horizontal OKN in parietooccipital infarcts. Impaired vertical OKN in PSP (downward jerks impaired when drum rotated upwards).
2. Pendular – Congenital or acquired, Multiple sclerosis, monocular vertical in case of visual loss. Oculopalatal myoclonus, oculomasticatory monorhythmia. Associated with oscillopsia, if acquired.
3. Jerk – Vestibular or neural lesion.
   (a) *Horizontal* – (i) Peripheral – Greatest amplitude away from side of lesion, with fast component always in the same direction. Lesion in labyrinth. (ii) Central – Greatest amplitude towards the lesion. Fast component in direction of gaze. Occurs with brainstem, vestibular nuclei or cerebellar lesions.
   (b) *Vertical* – Downbeat (first phase downwards in primary position, in cervicomedullary lesions, vestibulocerebellar lesions). Upbeat in midbrain, medulla and vermian lesions (Wernicke encephalopathy).
   (c) *Periodic alternating nystagmus* – Each cycle lasts 2–3 minutes. Lesions at cervicomedullar junction, medulla, nodule, uvula, MS.
   (d) *Rebound* – Cerebellum, medulla.
   (e) *Jerk nystagmus* – Slow drift of the target followed by a fast corrective saccade. Jerk nystagmus can be downbeat, upbeat, horizontal (left or right), and torsional
   (f) *Gaze evoked* – Most common type, in the direction of gaze. Impaired gaze holding. Causes – sedatives, anticonvulsants, brainstem and cerebellar lesions.
   (g) *Vestibular nystagmus* – Pure form in brainstem, vestibulocerebellar lesions. Mixed form in peripheral vestibular diseases.
   (h) *Convergence retraction nystagmus* – Bilateral adduction causing convergence and retraction of both eyes on looking upwards in Parinaud's syndrome, midbrain posterior commissure lesion.
   (i) *Ocular bobbing* – Conjugate eye movements with fast downward movement and slow drift back to the midline. Massive pontine lesions in comatose patients.
   (j) *Ocular flutter* – Intermittent bursts of back to back horizontal saccades without any intersaccadic interval. No vertical component.
   (k) *Opsoclonus* – Back to back saccades in multiple directions (horizontal, vertical). Associated with facial twitching, myoclonus, ataxia (dancing eyes and dancing feet). Cerebellitis, posterior fossa tumors, neuroblastoma, paraneoplastic, lithium, phenytoin.

TRIGEMINAL NERVE

Motor – (a) *Peripheral lesions* (between pons and Gasserian ganglion). All three divisions may be affected giving rise to: Weakness and wasting of muscles of mastication on affected side with deviation of jaw towards the affected muscles.

Causes – (i) Between pons and trigeminal ganglion: Inflammatory lesions such as meningitis, compression by tumour or aneurysm, degeneration as in tabes. (ii) Trigeminal ganglion – Tumours, e.g. meningioma, acoustic neuroma, fracture of middle cranial fossa, Gradenigo's syndrome (with 6th nerve), herpes zoster. (iii) After leaving the ganglion – Cavernous sinus or superior orbital fissure lesions, fracture of bones of face. (iv) Motor neuropathy in metastasis at skull base.

(b) *Central lesions* – Weakness of muscles of mastication with paralysis of external rectus and of face on affected side.

Causes – Tumours, syringobulbia, and vascular lesions involving pons, and uppermost cervical segments of spinal cord.

Sensory – 1. Impaired or absent corneal reflex. 2. Loss of sensation of half of face and scalp to light touch, pain and temperature but not to deep pressure pain. Also of palate and nose. Sensation of broken cup when patient drinks. 3. Taste may be impaired on anterior two-thirds of tongue. 4. Diminished secretion of tears and saliva on affected side. 5. Excessive furring of tongue on affected side.

Trigeminal Neuralgia (Tic Douloureux)

A disorder characterised by paroxysmal attacks of neuralgic pain with affection of one or more divisions of the trigeminal nerve. The pain involves the first and second divisions equally, and rarely the first. It rarely occurs bilaterally.

Aetiology

Age – usually after middle age. *Sex* –more in females. *Cause* – unknown. May entail a fault in the mechanism that insulates neurones from each other. Vascular compression of nerve root by an aberrant blood vessel.

Exciting causes – Spontaneous, or following exposure to cold wind, blow on face, or chewing, or eating, or drinking hot or cold fluid or talking, or washing the face.

Symptoms

During the attack

1. Pain – (i) Usually II and III division together. (ii) Severe in intensity. (iii) Sharp, shooting lasts less than 30 secs. (a) *Site* – Unilateral, more commonly confined to one of the three divisions of the nerve. Common points of origin are just external to alae nasi, infra orbital foramen or mental foramen below the canine tooth. Pain sometimes confined to one branch of a division. Tendency for pain to commence locally and subsequently spread in each attack, thus invading a larger area. (b) *Character* –sharp and paroxysmal, sudden in onset and cessation. Short lightning flashes of pain or "red hot needles". (c) *Duration* – only a few seconds. Rarely half a minute or longer due to series of short sharp stabs of pain, interrupted by brief intervals. The pain usually resolves after a few weeks but eventually recurs.
2. Associated symptoms – (i) During the attacks, the face is often thrown into a strong involuntary tonic spasm on the affected side. (ii) Flushing of face. (iii) Dilatation of pupil. (iv) Excessive lacrimation and (v) sometimes secretion of nasal mucus and saliva may occur on the side of pain.

In between the attacks

1. *Trigger zones* – Certain localised hyperaesthetic spots on face, gums or tongue, a slight stimulus of which sets off an attack.
2. *Dull continuous pain* – follows paroxysmal pains if severe. Usually of a boring character. Skin over affected region is sore and tender after a paroxysm.
3. *Sensory changes* – none except for hyperaesthesia.
4. *Skin and hair* – After repeated attacks skin becomes shiny and hair in the area may become grey or rubbed away.
5. *Loss of weight and depression* – due to interference with food intake and recurrence of pain over a prolonged period.

Differential Diagnosis of Facial Pain

1. ***Symptomatic trigeminal neuralgia*** – (a) Neuralgia indistinguishable from the idiopathic variety may occur as a result of compression of trigeminal root or ganglion, e.g. meningioma, acoustic neuroma, aneurysm of basilar artery, arteriovenous malformations, basilar invagination, epidermoid cholesteatomas in the cerebellopontine angle, as a result of Paget's disease or osteomalacia. (b) Paratrigeminal neuralgia (Raeder's syndrome) – Severe pain in and around one eye accompanied by Horner's syndrome on the affected side. It is continuous and progressive and is usually caused by a structural lesion, often malignant, in the base of the skull involving the paratrigeminal

region. (c) Multiple sclerosis – Diagnosis of multiple sclerosis should always be suspected in a young patient with trigeminal neuralgia. (d) Syringobulbia. (e) Painful superior orbital fissure syndrome (Tolosa-Hunt syndrome) – caused by granulomatous tissue involving nerves III, IV and VI. Pain with development of ocular palsies and loss of first division trigeminal sensation.

2. ***Referred pain*** – Paranasal sinuses, toothache, aural infection. Temporomandibular joint dysfunction (Costen's syndrome) – abnormality of bite and aggravated by chewing.
3. ***Vascular pain*** – (a) *Migraine* – Episodes of severe and continuous pain, often burning in character in or behind one eye, or in cheek, forehead and temple. Often suffusion of conjunctiva and blocking of nostril on that side. (b) *Temporal arteritis* – Pain of dull, throbbing nature with associated scalp tenderness. Thickened temporal arteries with reduced or absent pulsations.
4. ***Other neuralgias*** – (a) *Post-herpetic neuralgia* – Pain continuous in nature. Vesicles and scars of herpetic infection. (b) *Glossopharyngeal neuralgia* – Pain in tonsillar fossa, back of throat and larynx; may radiate to ear on affected side. Swallowing is the stimulus most likely to produce pain.
5. ***Atypical facial pain*** – Intermittent but long -lasting pain of aching character which affects the cheek and upper jaw, often bilateral and occurs almost exclusively in young and middle-aged women. Generally believed to be a manifestation of depression or anxiety.
6. ***Miscellaneous*** – (a) *Clonic facial spasm* – Sometimes painful, usually associated with intermittent twitching of eyelid and face on one side. Platysma usually involved in twitching. (b) *Neuralgic pain* – occasionally associated with facial hemiatrophy. (c) *Idiopathic trigeminal neuropathy* – Commonly associated with muscle wasting of masseter.

Management

1. Elimination of all possible sources of infection.
2. Drugs:
   (a) *Analgesics* – Potent analgesics must be used with caution because of danger of habituation.
   (b) *Carbamazepine* – Effective in relieving symptoms in majority of patients within 24 hours. Initial dose 100 mg t.d.s. gradually increased to 200 mg qds. or more. Side effects – dizziness and drowsiness common. Dryness of mouth, nausea and vomiting and erythematous rashes may occur but disappear within 48 hours after stopping treatment. Rarely depression of bone marrow. *Oxcarbamazepine* – alternative with equal efficacy and better side effect profile with less chances of bone marrow toxicity.
   (c) *Phenytoin sodium* – 0.1 gm t.d.s. when carbamazepine cannot be tolerated or
   (d) *Gabapentin* - 300 mg bd can be increased to 1,800 mg/day.
   (e) *Pregabalin* – 25 mg bd can be increased to 300 mg/day.
3. Injection of alcohol – into affected nerve, or the Gasserian ganglion, if more than one division is affected. Inject about 10 minims of 90% alcohol after local anaesthesia with 2–3 drops 2% procaine. Relief seldom lasts more than 6 months.

   Undesirable effects – Neuropathic keratitis, paresis of muscles of mastication lasting a few months, numbness or deadness in the skin of the face. Useful in those in whom on account of age or for some other reason surgery is contraindicated.
4. Microvascular decompression – Separation of blood vessels in contact with trigeminal nerve roots and insertion of nonabsorbable sponge gives relief from pain in most patients.
5. Radiofrequency thermocoagulation – of trigger spot or site of pain origin localised by electrical stimulation of needle inserted into trigeminal ganglion produces permanent relief.
6. Surgery – Selective or complete pre-ganglionic section of the trigeminal root. Indications - (i) Failure of repeated injections to give relief. (ii) Patient going abroad. (iii) To avoid necessity for repeated injections. Permanent relief from pain but disadvantages are permanent dysaesthesiae in most cases. A better technique is percutaneous electrocoagulation of the preganglionic rootlets corresponding to the trigger zone, the temperature of the probe being so regulated as to coagulate the small thinly myelinated pain fibres but preserving the more heavily myelinated touch fibres.

VII. FACIAL NERVE

Facial Weakness

General characteristics – Facial palsy can be due to upper or lower motor neurone involvement. Table 15 gives the dfferentiatig features between the two.

Lesions, Causes and Localization

Supranuclear

1. *Corticospinal lesion* –

   Causes – Tumour, abscess, haemorrhage or thrombosis. Signs – (a) Lesions in region of cerebrum, cerebral peduncles and upper pons – Facial palsy associated with paralysis of ipsilateral limbs.

   (b) Lesions in region of lower pons, prenuclear lesions – Facial palsy with crossed paralysis of limbs.

2. Mimic paralysis – Weakness or abolition of emotional movements of face with retention of voluntary movements due to lesions of anterior part of frontal lobe or lesions in neighbourhood of optic thalamus.

Nuclear and Infranuclear Lesions

Causes and features of nuclear and infranuclear facial palsy are given in Table 16.

Bilateral Lower Motor Neuron Facial Palsy

Causes of bilateral lower motor neuron facial palsy are given in Table 17.

Table 15: Differentiating features between upper and lower motor neueron facial palcy

Upper motor neuron	*Lower motor neuron*
Affect mainly muscles of lower part of face	Whole face affected
Never complete palsy	Complete palsy
Seldom isolated palsy	Isolated emotional movement
Loss of emotional movement	Emotional movement preserved
No muscle contracture	Marked muscle contracture may occur
No reaction of degeneration	Reaction of degeneration present
EMG and nerve conduction normal	Evidence of lower motor neuron lesion on EMG

Table 16: Causes and features of nuclear and infranuclear facial palsy

Site of lesion	*Possible causes*	*Associated features*
Pons [Fig. 7(1)]	Vascular lesions, tumour, multiple sclerosis, encephalitis, syringobulbia motor neuron disease,	5th nerve involvement – Sensory loss on opposite side and often paralysis of ipsilateral jaw muscles or 6th nerve involvement – Facial palsy with contralateral limb weakness
Cerebellopontine Angle [Fig. 7(2)]	Tumour in crebellopontine angle, e.g. acoustic neuroma, Meningioma	Nerve deafness, tinnitus, vertigo, cerebellar signs, loss of corneal reflex CSF changes
Temporal bone lesion		
Region of geniculate ganglion [Fig. 7(3)]	Trauma, herpes zoster of geniculate ganglion (Ramsay Hunt syndrome). Spread of infection from middle ear or mastoid	Variable deafness, vertigo Defective lacrimation Loss of taste on anterior 2/3 of tongue
Between geniculate ganglion and nerve to stapedius [Fig. 7(4a)]	Spread of infection from middle ear	Loss of taste on anterior 2/3 of tongue Hyperacusis Impaired salivary secretion
Between branching of nerve to stapedius and chorda tympani nerve [Fig. 7(4b)]		Facial motor paralysis Loss of taste on the anterior 2/3rd of the tongue Hearing is spared (no hyperacusis)
Within stylomastoid foramen (distal to branching of chorda tympani nerve) [Fig. 7(4c)]	Bell's palsy, suppurating glands, encephalitis, tetanus, acute inflammatory polyneuropathy, otitis media, mastoidectomy	Facial paralysis only
Peripheral nerve [Fig. 7(5)]	Tumour or inflammation of parotid gland, Sarcoidosis, Trauma, Parotid operation	Paralysis of some facial muscles only

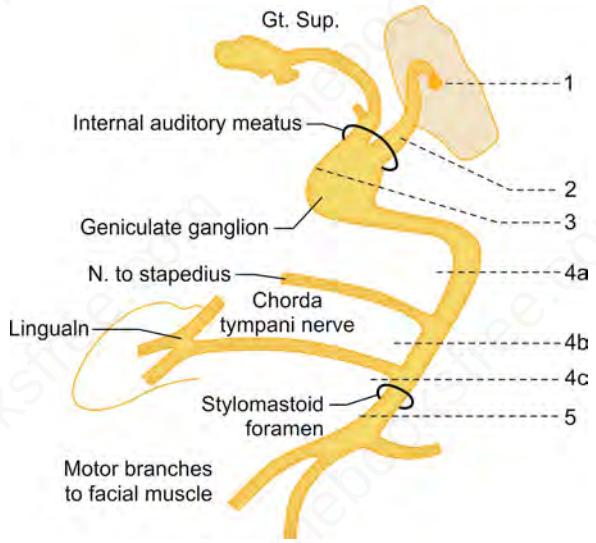


Fig. 7: Components of the facial nerve

Signs – Flattening of all normal folds, sagging of corners of mouth, fixed expression-less mask like face, no voluntary movements of facial muscles. Whites of eyes seen when patient attempts to close them. Patient talks as if he had severe stomatitis.

Bell's Palsy

Bell's palsy is an acute, apparently isolated, lower motor neuron facial palsy for which no cause can be found. Presumed to be viral due to HSV 1 (viral genomic sequences detected).

Aetiology

(a) *Associated known clinical conditions* – Diabetes, severe hypertension, last trimester of pregnancy, dental anaesthesia. (b) *Causes* – (i) Exposure to cold; oedema and subsequent compression of nerve trunk within the rigid Fallopian canal causes circulatory disturbance. (ii) Other important causes of acute facial palsy include suppurative otitis media, herpes zoster, head injury, Guillain-Barre syndrome, sarcoidosis and multiple sclerosis.

Symptoms

Sudden, following exposure to chill or without any apparent precipitating cause, maximum paralysis in 24 hours. Postauricular pain is common and may precede paralysis by 2 days. There may be spontaneous complaints of loss of sense of taste, hyperacusis and watering of the eye. Sweating less on affected side.

Table 17: Causes of bilateral lower motor neuron facial palsy

1. *Bilateral infranuclear lesions:*
– Guillain-Barre syndrome
– Leprosy
– Leukaemia
– Syphilitic or meningococcal meningitis
– Double otitis media
– Presumed to be viral due to HSV 1 genomic
– Post-diphtheritic
– Bell's palsy
– Uveoparotid paralysis.
2. *Muscle disease* – Myasthenia gravis/myotonic dystrophy, facioscapulohumeral dystrophy.

Signs

1. Forehead cannot be wrinkled; frowning lost (frontalis).
2. Eye cannot be closed (orbicularis oculi, sphincter of palpebral fissure). On attempting closure, eyeball turns upwards and outwards (Bell's phenomena).
3. On showing the teeth, the lips do not separate on affected side. Whistling not possible. Articulation of labial components difficult. Nasolabial fold flattened out. Angle of mouth on affected side droops with dribbling of saliva (Orbicularis oris, sphincter of oral fissure).
4. Cheek puffs out with expiration because of buccinator paralysis. Food collects between teeth and paralysed cheek. Fluid runs out while drinking (buccinator).
5. Base of tongue lowered (stylohyoid and posterior belly of digastric).
6. Vesicles within the external auditory meatus and ear drum in Ramsay Hunt syndrome. Pain may precede facial weakness. Deafness may result.

Investigation

Electromyography – of prognostic importance: (a) If signs of denervation after 10 days – Axonal degeneration, recovery incomplete or delayed. (b) If incomplete denervation in less than 7 days – Good prognosis. (c.) Fibrillation potential after 2 weeks suggests Wallerian degeneration.

Management

1. *Local heat* – Infra-red or moist heat, or short wave diathermy over face or parotid region or both, if there is tenderness of nerve trunk.

2. *Local treatment of muscles* – (a) The patient should massage the facial muscles with bland oil twice daily for 5 minutes. The massaging movements should start from the chin and lower lip and be directed upwards. With return of function the patient should practise movements of various muscles of face before a mirror. (b) Prevention of facial sagging – application of strips of adhesive tape to lift up the angle of the mouth. The tape is attached to the temple and extends down in a V shaped fashion to the upper and lower lips.
3. *Protection of eye* – with dark glasses or eye patch. The eye should be washed twice daily with mild zinc-boric solution to prevent conjunctivitis.
4. *Corticosteroids* – if seen within a week of the onset. Help by reducing secondary oedema. Prednisolone 40 mg daily for 4 days, reduced over next 6 days.
5. *Antivirals* – like acyclovir, valacyclovir or famciclovir in combination with steroids, if started within 3 days of onset.
6. *Surgery* – Decompression of facial nerve in second or third week cannot influence favourably natural course of Bell's palsy. In cases which fail to recover after 9 months anastomosis of facial with accessory or preferably hypoglossal nerve may be considered, or plastic surgery in cases of total paralysis with atrophy of musculature.
7. *Treatment of sequelae* – (a) Residual severe weakness – plastic surgery. (b) Faulty reinnervation resulting tears pouring from affected side on chewing (syndrome of crocodile tears) – cutting of tympanic nerve which normally conveys the glossopharyngeal salivary fibres.

VIII. AUDITORY NERVE

Cochlear Branch

1. Tinnitus. 2. Nerve deafness. Causes – (a) *At cochlear level* – Otosclerosis, Meniere's syndrome, drugs such as salicylates, streptomycin, quinine, prolonged exposure to noise. (b) *In nerve trunk* – Old age, inflammatory or toxic lesions, cerebellopontine angle tumours. (c) *In brainstem* – Pontine vascular lesions, severe demyelination, rarely tumours.

Tests of Function

(i) *Whispered or spoken voice* - The distance at which spoken or whispered voice is determined. The distance being noted, the examiner compares the patient acuity of hearing with his own.

Table 18: Rinne and Weber test

Test	*Normal*	*Conduction*	*Sensory neural deafness deafness*
Rinne	AC > BC	BC > AC	AC > BC (both are reduced)
Weber	Not lateralized	Localized to poorer ear	Lateralized to better ear

(ii) *Tuning fork tests* – Rinne and Weber tests are useful in differentiating between conduction and sensorineural deafness (Table 18).

Vestibular Branch

1. Vertigo.
2. Nystagmus.
3. General symptoms such as sweating, nausea, vomiting.

Tests of Function

- Stance and gait. In presence of unilateral disturbance of vestibular function, patient tends to reel towards the affected side
- Positional testing for nystagmus. Patient will complain of vertigo and develop nystagmus within 10 seconds of head movement in presence of disorder of the labyrinth or its vestibular connections.
- Caloric tests allow one to investigate labyrinthine function in each ear based on the fact that the cupola can be deflected by currents setup in the semicircular canals if they are heated or cooled. Nystagmus - cold opposite, warm same (cows). The test can be performed on the opposite side after an interval. The test is particularly valuable in unconscious patients and must be performed in every case of coma.
- Stepping test involves marching for 50 steps at normal walking speed. If there has been more than 30° in body rotation or more than 1 meter of displacement from the starting point, it is suggestive of vestibular dysfunction.
- Past-pointing (Refer cerebellar disorders).

Tinnitus. Patient complains of subjective sensation of noises in the year (ringing, whistling, buzzing, roaring). It is usually accompanied by deafness. Causes: (a) Local: Peripheral impairment of function of conducting apparatus of the ear, e.g. wax in the year, catarrh of Eustachian tube, acute labyrinthitis. (b) Systemic: Drugs like quinine, salicylates; fever, severe anemia, AR. (c) Central auditory nerve tumour, aura of epilepsy, temporal lobe or brainstem lesions.

IX, X. GLOSSOPHARYNGEAL AND VAGUS NERVE

Disorders

1. *Paralysis of palate* – (a) Unilateral paralysis: No symptoms. Positive 'Ah' test. (b) Bilateral paralysis – Nasal regurgitation, nasal twang, no elevation of palate on phonation.
2. *Posterior Pharyngeal wall weakness* – (a) Unilateral – Pharyngeal wall droops on affected side. (b) Bilateral – Marked dysphagia.
3. *Pharyngeal* gag reflex is tested by stimulating the back of the throat. The afferent arc of the reflex is the 9th Cr. nerve, the efferent arc 10th Cr. Nerve. If there is no elevation of the palate when patient says 'ah' but there is elevation, during the gag reflex, there is an UMN lesion. If both volitional and reflex activities are absent, there is likely to be LMN lesion or muscle lesion.
4. *Movement of Larynx* - whilst patient is made to swallow some water, the force of upward movement of the larynx is assessed digitally.
5. *Voice and ability to cough* - Paralysis of one vocal cord (the cord lying in the midline) leads to hoarseness, low tone voice and inability to cough explosively (bovine or gander cough).
6. *Vocal cords* may be examined with a laryngoscopic mirror. The vocal cord on the affected side lies immobile midway between abduction and adduction.

Causes of laryngeal paralysis – (a) Nuclear lesions – Syringobulbia, posterior inferior cerebellar artery thrombosis, encephalitis, progressive bulbar paralysis, diphtheria. (b) Tumours, meningovascular syphilis, extension of infection from middle ear. (c) Trunk – Penetrating wounds and tumours. (d) Recurrent laryngeal nerve – Aortic aneurysm, enlarged left atrium, mediastinal mass or glands, enlarged thyroid, carcinoma of oesophagus.

XI. ACCESSORY NERVE

Cranial portion – Same as nuclear lesions of vagus – paralysis of palate, pharynx and larynx.

Spinal branch – Paralysis of sternomastoid (weakness of rotation to opposite side) and of upper fibres of trapezius (lowering of shoulder, winging of scapula). The supranuclear connections act on the ipsilateral sternomastoid (turning the head to contralateral side) and on contralateral trapezius. This results in head turning away from the relevant hemisphere during a seizure, and turning towards the relevant hemisphere with cerebral infarct.

Causes – (a) *Nuclear lesions* – Poliomyelitis, motor neuron disease, syringomyelia, cervical spinal cord tumours. (b) *Lesions of nerve trunk* – (i) Within posterior fossa–Tumours near jugular foramen, granulomatous meningitis or basal carcinoma (usually with 9th, 10th, and 12th nerves). (ii) After exit from the skull – Compression by enlarged deep cervical glands, or injury by penetrating wounds or during operations in cervical region.

XII. HYPOGLOSSAL NERVE

1. Unilateral paralysis – Wasting of tongue. Tongue becomes sickle shaped with concavity on paralysed side. Deviation towards paralysed side on protrusion.
2. Bilateral paralysis – Marked wasting, protrusion not possible. Fasciculations if progressive bulbar paralysis. Dysarthria. In pseudobulbar palsy tongue is somewhat smaller than normal owing to spastic contraction of the muscles.

Causes

(a) *Unilateral lower motor neuron lesions* – (i) Hypoglossal nucleus or fibres of the nerve in the course through medulla – Poliomyelitis, syringobulbia, thrombosis of median branches of vertebral artery. (ii) Between medulla and hypoglossal canal – Glomus tumour, meningioma or aneurysm of vertebral artery, granulomatous or carcinomatous meningitis. Congenital anomalies in neighbourhood of foramen magnum, e.g. basilar impression. Periostitis of hypoglossal canal. Rarely head injury.

(b) *Bilateral lower motor neuron lesion* – Progressive bulbar paralysis.

(c) *Bilateral upper neuron paralysis* – Pseudobulbar palsy due to double hemiplegia, multiple sclerosis, motor neuron disease, tumours of brainstem.

4. PUPILLARY DISORDERS

Pathway of pupillary constriction and light reflex (Parasympathetic).

Afferent impulse – such as bright light shone in one eye carries it through the optic nerve to midbrain and from here to Edinger Westphal nucleus on same and opposite side, through the posterior commissure.

Efferent fibres – leave in oculomotor nerve, pass to ciliary ganglion and then to short ciliary nerve, to the constrictor fibres of sphincter pupillae. Shining a light in one eye will constrict both pupils to an equal degree provided all pathways are intact.

Pathway of pupillary dilatation – (Sympathetic) – Fibres descend from the hypothalamus through lateral portion of brainstem into the spinal cord. Pupillary fibres pass out in anterior roots of C8, T1, enter the sympathetic chain and in the superior cervical ganglion give rise to postganglionic fibres which enter the cranium along the wall of the internal carotid artery. The fibres then pass through the ciliary ganglion to the iris or join the cranial nerves III, IV, V and VI running to the eye and iris.

PUPILLARY ABNORMALITIES

1. ***Position*** – may be congenitally eccentric. Sometimes ectopic pupil in midbrain lesions.
2. ***Irregularity*** – Slight irregularity (anisocoria) may occur in (i) healthy subjects, (ii) coloboma, operative procedures, synechiae or acute glaucoma, (iii) neurosyphilis.
3. ***Inequality*** – (i) Encephalitis sometimes. (ii) Intracranial haemorrhage. (iii) Aneurysm of aorta. (iv) GPI. (v) Third nerve lesions. The abnormal pupil will be smaller when it is dilated and larger when it is constricted.
4. ***Dilatation*** (Mydriasis) –
   - *III N lesion* – Refer.
   - *Drugs*–Mydriatric drops, amphetamine, glutethimide, atropine, cocaine, dhatura poisoning.
   - *Tonic pupil* (Holmes-Adie syndrome) – Benign condition usually occurring in young women. Unilateral dilated pupil, reacts promptly to mydriatics and miotics, but very slowly to light and accommodation, the larger pupil becoming smaller than its fellow. When the pupil is associated with sluggish or absent tendon reflexes, it is called Holmes-Adie syndrome. Cause is unknown.
   - *Optic atrophy* – producing blindness.
   - *Asphyxia and deep anaesthesia*.
   - *Parinaud's syndrome* – Dilated fixed pupil with loss of upward gaze.
5. ***Constriction*** (Miosis) –

   (a) Horner's syndrome – (i) Miosis – Affected pupil smaller than opposite pupil. (ii) Ptosis –Drooping of eyelid (less marked than with III N palsy). (iv) Enophthalmos. (v) Absence of sweating (if lesion proximal to fibre separation along internal and external carotid arteries).

   Causes – Sympathetic damage at sites listed in Table 19.

Table 19: Sympathetic damage at various sites and causes

1. Preganglionic	Tumour (glioma)
	Vascular lesion - Lateral medullary syn. Syringobulbia
2. Cervical cord	Tumour
	Syringomyelia
3. Ant. roots C8, T1	Tumour, e.g. neurofibroma
	Lower brachial plexus palsy
4. Cervical	Pancoast tumour
sympathetic chain	
5. Post-ganglionic	Int. carotid occlusion, dissection
	Middle fossa lesions (tumour, granuloma)

   Raeder's paratrigeminal syndrome – Painful Horner's syndrome with involvement of one or more cranial nerves (II to VI) and orbital sympathetic supply, usually pain in V nerve distribution.

   (b) Argyll-robertson pupil – (i) Miosis, generally bilateral. (ii) Irregular. (iii) Does not react to light either directly or consensually. (iv) Reaction to accommodation is instantaneous. (v) Reacts slowly and unevenly to atropine or homatropine. (vi) Stroma of iris may show loss of pigment or actual atrophy. (vii) Failure of pupils to dilate to painful stimuli.

   Causes – (i) Neurosyphilis especially tabes dorsalis. (ii) Brainstem encephalitis. (iii) Multiple sclerosis. (iv) Cerebral tumour in region of third ventricle, aqueduct of Sylvius or corpora quadrigemina. (v) Syringomyelia. (vi) Chronic alcoholism. (vii) Diabetes. (viii) Following infectious mononucleosis.
6. ***Failure of accommodation*** – (i) Selective impairment in lesions of third nerve or ciliary ganglion, or diphtheria. (ii) Parkinson's disease. (iii) Brainstem lesions such as tumours or encephalitis.
7. ***Absent light reflex*** – Third nerve lesions, AR pupil, glaucoma, iritis, cataract.
8. ***Wernicke's pupil reaction*** – Absence of pupillary contraction when a ray of light is thrown on the blind side of the retina, whilst illumination of the seeing half of each retina still evokes a normal light reflex. It signifies a lesion in the visual path in the optic tract.
9. ***Marcus Gunn pupil*** (pupillary escape). On stimulation of normal eye by bright light there is no abnormality; when affected eye is stimulated reaction is slower, less complete and very brief so that the pupil may start dilating again (pupillary escape phenomena). Seen particularly in optic nerve damage due to multiple sclerosis.

10. ***Pupillary abnormalities in unconscious patient*** – Refer Coma.
11. ***Other light-near dissociation syndromes*** – Pupils do not react to light, react on accommodation. Pupils of normal size, vision intact. Causes –Neurosyphilis, diabetes, high midbrain lesions, pinealoma, multiple sclerosis. Bilateral optic atrophy.
12. ***Miscellaneous pupillary reactions***
    (a) *Hippus* – Rhythmic contractions of the iris, regular in periodicity and visible to the naked eye, causing the pupils to alternately dilate and contract. Causes – (i) Normal in some. (ii) Rheumatic chorea. (iii) Multiple sclerosis. (iv) Brain tumour sometimes. (v) Alcoholic subjects. (vi) Unilateral in paralysis of IIIrd nerve.
    (b) *Paradoxical pupillary reaction* – Pupils dilate instead of contracting on exposure to light. Not uncommon in tabes.
    (c) *Ciliospinal reflex* – Reaction of pupil to painful stimulus of skin of neck causing the pupil to dilate; it is often absent in the early stages of tabes and in cervical sympathetic palsy.

5. SENSORY IMPAIRMENT

CONDUCTION OF SENSORY AFFERENT IMPULSES

All forms of sensation – travel via a peripheral nerve and a sensory root to the spinal cord, or the brainstem (Fig. 8).

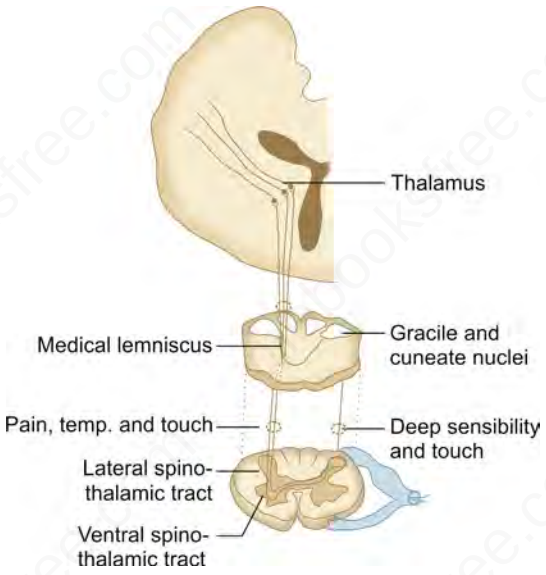


Fig. 8: Diagram showing course of sensory paths to the thalamus and from there to the cerebral cortex

Touch – Fibres carrying sense of light touch ascend the posterior columns on the same side as they enter, up to nuclei gracilis and cuneatus. Further fibres then cross the midline to ascend the brainstem in the medial fillet, being here joined by touch fibres from the face. They then pass to the thalamus and on to the post-Rolandic cortex. Other elements of touch on entering the cord ascend several segments, and then cross to the opposite side, enter the lateral spinothalamic tract, ascend this tract and end in the posterolateral ventral nucleus of the thalamus.

Pain and temperature – are transmitted only through short posterior root fibres which terminate in posterior horn at the level of root entry and 2 to 4 segments higher. Neurones of the second order cross to the opposite side, enter the lateral spinothalamic tract, ascend this tract and end in the posterolateral ventral nucleus of the thalamus. From the thalamus, sensory impulses pass through the posterior limb of the internal capsule and the thalamoparietal radiations to the post-Rolandic cortex. However lesions at cortical level cause little disturbance of pain and temperature.

Deep sensibility (appreciation of position and movement) – is conveyed centrally by way of long posterior root fibres which ascend in the ipsilateral posterior column. These fibres terminate about cell bodies in the gracile and cuneate nuclei, the fibres of which pass across the median plane and ascend in the medial lemniscus to the posterolateral ventral nucleus of the thalamus. A relay from the thalamus extends to the post-central gyrus of the parietal lobe.

Lesions confined to purely cutaneous nerves do not alter deep sensibility because in the peripheral nervous system the fibres subserving deep sensibility pass only in the nerves that supply muscles.

Localization of lesion – of disturbances of sensation.

SENSORY CORTEX LESIONS

1. Extreme variability of response to sensory stimuli.
2. Impairment of appreciation of posture and passive movement, light touch, and discrimination of two compass points.
3. Affection of appreciation of size, shape, form, roughness and texture of objects (astereognosis), ability to distinguish between different weights (barognosis) and ability to recognise symbols written on the body, usually palms (graphaesthesia).
4. Qualitative recognition of pain, heat and cold preserved but in dealing with thermal stimuli, e.g., heat, it may be difficult to say which of the two is hotter.
5. Difficulty in appreciating intensity of stimuli.

SUBCORTICAL LESIONS

1. Hemianaesthesia affecting the contralateral face, upper and lower limbs.
2. Sensory loss severe and extensive.
3. No variability of response and threshold as in cortical lesions.
4. No alteration in appreciation of qualitative pain, heat and cold.
5. Astereognosis and loss of appreciation of position, passive movement, and tactile localization.

THALAMIC LESIONS

1. Gross impairment of all forms of sensation on opposite side of body if lesion extensive.
2. Loss of appreciation of posture, passive movement, and often of light touch.
3. Threshold for pain raised with exaggerated response to painful stimuli (hyperpathia).

BRAINSTEM LESIONS

1. *Lateral* – Hemianalgesia and thermoanaesthesia on opposite side of body. Intact postural sense, appreciation of passive movement and tactile discrimination.
2. *Lesions of medulla* – affecting the descending root of Vth nerve, and ascending spinothalamic tract from the rest of the body, e.g. posterior inferior cerebellar artery thrombosis – Loss of pain and temperature on one side of face and opposite side of body.

SPINAL CORD LESIONS

1. *Total cord lesion* – Bilateral loss of all forms of sensation below a definite level. The upper level of the lesion may be indicated by a zone of hyperaesthesia.
2. *Hemisection of spinal cord (Brown-Sequard syndrome)* – Common causes are compression of cord, intramedullary neoplasms, sometimes due to stab in the back, bullet-wounds, vertebral fractures or caries, vascular causes, arachnoiditis. *Cl. Fs.* – Contralateral loss of pain and temperature, ipsilateral loss of proprioception. At the highest level on the side of lesion there is a band of analgesia due to involvement of the root entry zone.
3. *Central (intrinsic) cord lesions* – e.g. syringomyelia or intramedullary tumours. Dissociated anaesthesia, i.e. loss of pain and temperature and preservation of proprioception and 'discriminatory' sensation.
4. *Dorsal column lesions* – e.g. subacute combined degeneration. (a) Loss of proprioception and vibration sense leading to ataxia. (b) Loss of deep pain (loss of tenderness of tendo-Achilles). (c) Positive Rombergism (ataxia occurs with eyes closed but not when they are open). (d) Hypotonicity (many spinocerebellar fibres travel in the posterior columns before entering the spinocerebellar tract).
5. *Posterior root entry zone* – e.g. tabes dorsalis. Severe sensory ataxia, impaired tactile discrimination, and impairment of deep pressure sensation, and of position, joint and vibration sense.
6. *Conus medullaris* – There is loss of sensation in the saddle area – upper and inner thigh and perianally. Involvement of the roots of cauda equina produces loss of sensation along the roots involved along with involvement of deep reflexes. The plantar is never extensor in conus medullaris or cauda equina lesions.

PERIPHERAL NERVE LESIONS

1. *Polyneuropathy* – Peripheral loss of sensation affecting both hands and feet (glove and stocking anaesthesia).
2. *Lesion of sensory root* – Loss of all forms of sensation over a clearly defined dermatome in one part of body only.

Hysterical – Anaesthesia of "glove and stocking" distribution of the limbs. Unlike polyneuropathy, there is an abrupt line of demarcation between the area of complete sensory loss and that where all sensation is normal. Areas of spurious sensory loss may be found elsewhere, e.g. over one-half of the skull. Reflexes are not diminished.

6. THE REFLEXES

DEEP REFLEXES

Figure 9 shows components of the spinal reflex mechanism of the quadriceps reflex (knee jerk). Table 20 gives causes of absent deep reflexes

A – afferent path;
B – efferent path;
C – pathway of cerebral inhibition.

Causes of exaggeration – Organic lesion of pyramidal tract, tetanus, strychnine poisoning, fright, anxiety.

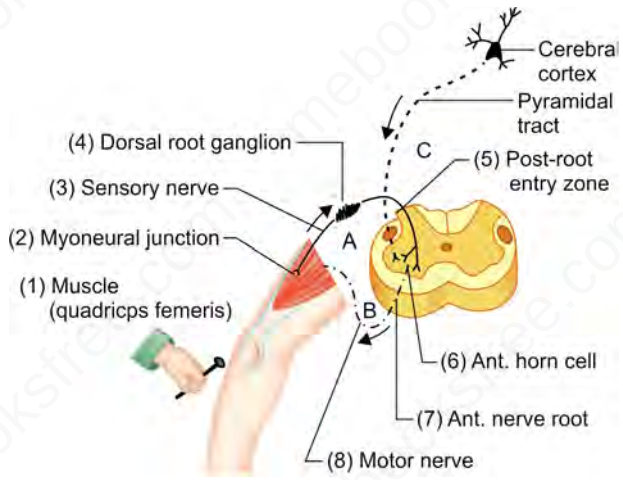


Fig. 9: Components of the spinal reflex mechanism of the quadriceps reflex (knee jerk)

Table 20: Causes of absent deep reflexes

A. Focal lesions within reflex
1. Muscles – Myopathies, periodic paralysis.
2. Sensory nerves – Sensory polyneuritis, e.g. diabetes.
3. Posterior root ganglion – Herpes zoster of 3rd or 4th lumbar segment.
4. Posterior root entry zone – Tabes, subacute combined degeneration.
5. Anterior horn cells – Poliomyelitis, progressive muscular atrophy.
6. Anterior nerve root – e.g. tumour, spondylitis, radiculopathy.
7. Peripheral motor nerve – e.g. diphtheria, trauma.
B. Lesions outside the spinal reflex
1. State of cerebral or spinal 'shock' which occurs immediately after a severe cerebral catastrophe or spinal injury.
2. Muscle contracture – will produce depression in deep reflexes.
3. Normal individuals unable to relax.

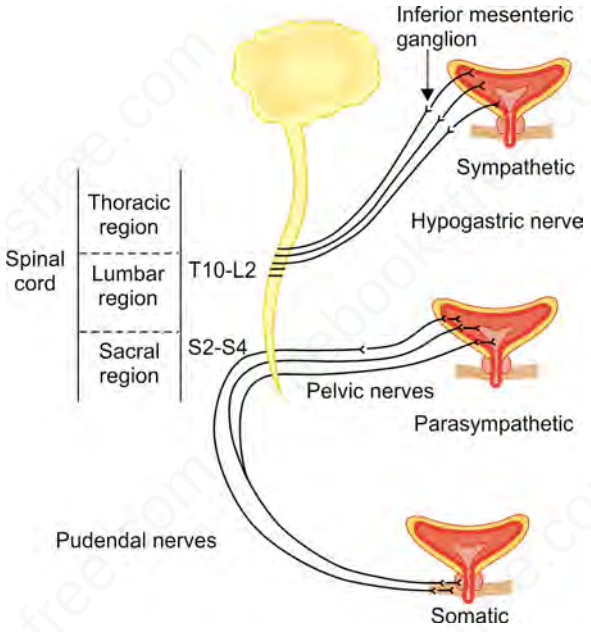


Fig. 10: Innervation of the lower urinary tract

Table 21: Neurological causes of voiding dysfunction

Suprapontine causes
• Cortical causes
– Frontal lobe lesions
– Normal-pressure hydrocephalus (NPH)
– Cerebrovascular accident (ACA territory)
– Frontal tumors
– Dementia
Infrapontine causes
• Spinal cord injury
• Multiple sclerosis
• Neoplasms (metastatic, primary)
• Tropical spastic paraparesis (HTLV-I)
• A-V malformations
• Cervical myelopathy
• Myelitis
Subsacral causes
• Tethered cord
• Spina bifida
• L4-L5 central disc prolapse
• Cauda equina lesions – ependymoma, neurofibroma
Others
• Multiple system atrophy

7. NEUROLOGICAL DISTURBANCES OF BLADDER AND BOWEL

BLADDER DISORDERS

The two functions of the bladder are storage and voiding. Normal bladder control requires intact spinal connections between the pontine micturition centre and the sacral spinal cord (S2, S3, S4) (Fig. 10). The pontine centre receives input from higher centres, particularly the medial aspects of the frontal lobe. Disruption of spinobulbospinal micturition reflex pathway results in impaired storage and/or voiding. Neurological causes of voiding dysfunction are listed in Table 21.

TYPES OF BLADDER DISTURBANCES (NEUROGENIC BLADDER)

I. *Upper motor neuron lesion* (Spastic neurogenic bladder). Bladder capacity is reduced and there are involuntary detrusor contractions. Infantile type of reaction with urgency. Detrusor sphincter dyssynergia. Detrusor instability:
   1. *Cerebral lesions (Cortical bladder)* – (a) Patient voids in inappropriate places (frontal lobe incontinence, uninhibited bladder). (b) Associated mental deficiency. Usually patient is not aware of having soiled his clothes. Infection is common. There is complete emptying of bladder.
   2. *Spinal cord lesion (Spinal bladder)*:
      (a) *Acute transection of spinal cord* – (i) Flaccid paralysis of bladder (denervated bladder). Bladder rapidly becomes distended and there is retention with overflow incontinence. (ii) Later as spasticity develops (as also spasticity in the legs), the bladder becomes spastic and contracted. Distension produced by accumulated urine provokes reflex contraction (automatic or reflex bladder). The bladder can be emptied by manual pressure. But contrary to cortical bladder emptying is incomplete.
      (b) *Incomplete lesion of cord* – e.g. compression, multiple sclerosis, trauma. (i) Weak voluntary control remains. (ii) Urgency and precipitancy of micturition and difficulty in both initiating and inhibiting bladder action. (iii) Sensation of bladder filling and distension may or may not be present depending on whether or not sensory tracts are interrupted.

II. Lower motor neuron lesions (Atonic or autonomous neurogenic bladder) – Lesion in micturition centre of cord, cauda equina, sacral roots, or interrupting sacral reflex arc. (i) Continuous dribbling incontinence. (ii) Micturition can be initiated by suprapubic pressure. (iii) High infection risk.
   1. *Posterior root lesions* (Sensory bladder) – e.g. tabes dorsalis, subacute combined degeneration, diabetes. Break of reflex arc on afferent side. (i) Bladder both insensitive and hypotonic, and overfills without patient being aware of it. (ii) Urine can be voided by considerable straining but evacuation is incomplete. (iii) Patient can initiate micturition as motor component is normal.
   2. *Anterior root lesions* – Herniated disc or sacral cord lesions - e.g. spina bifida, tumour. Break of reflex arc on efferent side. Bladder partially paralysed (paralytic bladder) and hypotonic. There is painful distension of bladder but inability to initiate or continue micturition. In later stages there is compensatory distension of bladder and overlow incontinence.

Table 22 shows main types of bladder neurogenic dysfunction.

INVESTIGATIONS

(a) *Post-micturition residue estimation* – using ultrasonography or catheterization; a residue of more than 100 ml is most likely to contribute to bladder dysfunction. (b) Dynamic tests involving assessment of lower urinary tract for assessing detrusor behaviour. The tests involve measuring pressure-volume relationship during bladder filling and micturition using cystometrography and a voiding study. (c) Patients at risk of upper tract disease should be assessed by *iv urography* and, if indicated follow-up *isotope renography*.

Table 22: Types of bladder neurogenic dysfunction

	Uninhibited bladder	*Spinal bladder*	*Cauda equina lesions*	*Sensory bladder*
Lesion	Higher cerebral centres in frontal lobe	Spinal cord above sacral	Cauda, pelvic nerves	Posterior columns, posterior roots involving sacral segments
Sensation	Normal	Normal	Pain, paraesthesiae in low back. Sacral, perineal	None
Residual urine	Nil	>100 mL	+	+++
Bladder capacity	Normal	Reduced	Bladder large	Large bladder
Voiding evacuation	Sudden uncontrollable inappropriate urge incontinence	Sudden and uncontrollable reflex, urgency and frequency Urgent incontinence incomplete emptying	Straining or dribbling Stress incontinence	Straining and dribbling

MANAGEMENT

Impaired emptying – A permanent indwelling catheter can be used, or patient taught to perform intermittent self-catheterization.

Impaired storage – Oxybutynin hydrochloride has both anticholinergic and musculotropic actions. Dosage: initial 2.5 mg b.d. with gradual increase.

Other treatment – Desmopressin 20 µg intranasally has antidiuretic effect and hence circumvents the problem of volume-determined detrusor hyper-reflexia.

Faecal incontinence – may be caused by loss of voluntary control over the pelvic floor. Cauda equina or a more selective injury may lead to pelvic floor weakness. Surgery may be required for sphincter or post-anal repair. Symptomatic treatment with constipating agent (e.g. loperamide) helps if no cause is found.

8. INVOLUNTARY MOVEMENTS

EPILEPSY AND CONVULSIVE MOVEMENTS

1. ***Fits or convulsions*** – are motor manifestations of epileptic seizure. Epileptic seizure is a sudden abnormal, excessive paroxysmal discharge rising from repetitive neuronal firing in the cortex – Grand mal, petit mal, focal cerebral seizures, etc (See Epilepsy).

Table 23: Causes of myoclonus

Physiological myoclonus – A phenomenon occurring at onset of sleep (Hypnic jerks).
Pathological myoclonus:
a. *Myoclonus occurring in epilepsy*
– Myoclonic static epilepsy
– LG syndrome
– Juvenile myoclonic epilepsy
b. *Progressive myoclonus*
– Familial disorders – Tay-Sachs disease, Lafora body disease, Gaucher's disease, Ramsay Hunt syndrome, benign polymyoclonus.
– Subacute sclerosing encephalitis
– Creutzfeldt-Jakob disease
– Alzheimer's disease.
c. *Metabolic disorders*
– Renal, hypoxic or hepatic encephalopathy
– Hyponatremia
– Hypocalcemia
– Alcohol and drug withdrawal.

2. ***Myoclonus*** – Sudden, brief, shock-like jerks. Muscles of face and limb are mainly affected. Movements may be stimulated by visual, auditory or tactile stimuli.

   Types of myoclonus

   Focal myoclonus – These myoclonic jerks may arise from the cerebral cortex, brainstem, spinal cord or peripheral ns. Cortical myoclonus is a form of focal motor seizure. If repetitive and regular, it is synonymous with epilepsia partialis continua. Brainstem myoclonus (palatal myoclonus) is a regular, slow, rhythmic movements of the palate and sometimes ocular, facial and diaphragmatic muscles.

   Multifocal or generalized myoclonus – usually arises from the brainstem and may be stimulus sensitive, especially to sound. Table 23 gives causes of myoclonus.

   Management - treatment of underlying condition. Drugs can be used are GABAergic Valproic acid, Clonazepam, Levetiracetam, Primidone, Piracetam.

3. ***Opisthotonus*** – Extreme hyperextension of neck and spine varying from arching of spine to a state of rigidity so marked that only heels and vertex touch the bed.

   Causes – (i) Meningeal irritation, usually in children, (ii) extreme extrapyramidal rigidity, e.g. late stages of subacute encephalitis, (iii) tetanus, (iv) pontine hemorrhage secondary to tentorial pressure coning, (v) brainstem encephalitis, (vi) drugs – Dopamine blockers, (vii) hysteria.

MOVEMENT DISORDERS

1. ***Chorea*** – Involuntary, irregular random nonstereotype, purposeless, nonrhythmic, abrupt, rapid, unsustained, jerky movements that flow from one part to the other. Table 24 for the causes of chorea.

Table 24: Causes of chorea

Hereditary neurological disorders
• Huntington's disease
• Benign familial chorea
• Paroxysmal choreoathestosis
• Wilson's disease
• Neuroacanthocytosis
Other causes
• Kernicterus
• Levodopa
• Phenytoin, carbamazepine toxicity
• Infections – Tuberculoma, toxoplasma in HIV
• Antiphospholipid antibody syndrome
• Cerebrovascular – Basal ganglia (caudate, thalamus) infarct/ hemorrhage

Table 25: Types of dystonia

1. Single part of body.
2. Segmental – Two or more contiguous parts of body, e.g. cranial dystonia (Meige syndrome) with blepharospasm, oromandibular dystonia and sometimes cervical dystonia.
3. Generalized dystonia – Segmental plus other areas (leg plus trunk).
4. Multifocal – Two or more noncontiguous parts of body.
5. Hemidystonic – affecting one half of the body.

2. ***Dystonia*** – Movements that are sustained, frequently twisting, repetitive patterned causing abnormal posturing due to contraction of agonist and antagonist muscles. Progress from action induced and specific to occurrence at rest and generalized. May be slow or shock like (myoclonic dystonia).

   Table 25 for the types and Table 26 for the causes of dystonia.

   Diagnosis and investigation – When focal brain lesions are identified, the basal ganglia particularly the putamen or rostral midbrain is usually involved. The most common cause is primary torsion dystonia (PTD). Dopa-responsive dystonia (DRD) and some secondary dystonias (e.g. Wilson's disease) are treatable and must be excluded.

   Management – BOTOX (Botulinum toxin) injection into affected muscles under EMG guidance every 3 months provides symptomatic relief useful in focal dystonia. Wilson's disease should be ruled out in young patients. High dose central anti-cholinergic (trihexphenidyl: 20–120 mg/day) useful in children. Tetrabenazine 25–75 mg can be used with low dose titration.

3. ***Ballismus*** – Wild, rapid, flinging movements usually affecting the proximal joints of one arm, occurring constantly or with short remissions. Absent during sleep. Movement may be confined to one limb (monoballismus), one side (hemiballismus), or all the limbs.

   Cause – The most common cause is a partial lesion (infarct or hemorrhage) in the STN, but cases can also be seen with lesions in the putamen, thalamus and parietal cortex. Structural lesions like granulomas

   Treatment – Hemiballismus (hemichorea) may be controlled by therapy with tetrabenazine 25 mg bd or haloperidol 1.5–3 mg tds.

4. ***Tremors*** – Most common disorder is a rhythmic and regular movement that affects one or more body parts like limbs, neck, tongue, chin or vocal cords due to alternate or simultaneous contractions of agonists and antagonists. Two main types based on phenomenology are rest and action tremors. Table 27 gives classification of tremors:

Table 26: Causes of dystonia

1. *Primary (idiopathic) dystonia* – Pure dystonia.
2. *Dystonia plus syndromes*
– Neurochemical disorders (dopamine responsive dystonia, myoclonus dystonia, dystonia plus Parkinsonism)
– Huntington's disease
– Wilson's disease
– Corticobasl degeneration.
3. *Secondary dystonia* – due to structural brain damage.
– Perinatal cerebral injury
– Kernicterus
– Encephalitis
– Head trauma
– Thalamic lesions
– Antiphospholipid syndrome
– Focal cerebrovascular lesions/stroke
– AVM
– Hypoxic injury
– MS
– Posterior fossa tumors
– Cervical cord lesions, syringomyelia
– Toxins – Mn, Co, methanol
– Hypoparathyroidism
4. *Heredodegenerative* diseases (never pure dystonia)
– X-linked recessive: Lubag
– X-linked dominant – Rett syndrome
– AD – Juvenile Parkinsonism
- HD (usually chorea)
- DRPLA
- SCA 3
– AR – Wilson's disease (with tremor, Parkinsonism)
– MLD
– Lesch Nyhan syndrome
– Ataxia telangiectasia
– Friedreich ataxia
– Neuroacanthocytosis
– HSP with dystonia
– Juvenile neuronal ceroid lipofuscinosis
– Niemann-Pick type (dystonic lipidosis)
– Homocystinuria
– Hartnup disease
– Glutaric acidaemia
Neurodegeneration with brain iron accumulation (PKAN)

Contd...

Contd...

Mitochondrial diseases
Leigh disease
Leber disease
With parkinsonian syndromes
Idiopathic Parkinson's disease, PSPP,
CBGD

A. Physiological – Fine, of a part of the body occurring under stress (usually hand and feet).

B. Pathological tremors – Selective distribution, e.g. proximal or distal limb muscles groups, trunk or face, slower rate and disappearance during sleep.

   (a) *Tremor at rest* – Parkinson's disease, Parkinson's syndrome (drug-induced, post-encephalitic, CO poisoning); multiple sclerosis, trauma.

   (b) *Postural tremor* – Tremor that is most obvious on maintaining a position as in holding the arms outstretched – (i) Exaggerated physiological tremor – Anxiety, thyrotoxicosis, alcohol, caffeine, drugs, e.g. bronchodilators, tricyclic antidepressants, lithium, heavy metals (e.g. mercury). (ii) Structural brain disease – Wilson's disease, severe cerebellar disease, neurosyphilis, multiple sclerosis. (iii) Benign essential familial tremor.

   (c) *Intention or action tremor* – Brainstem or cerebellar dysfunction – Multiple sclerosis, spinocerebellar degeneration, drugs (e.g. phenytoin), stroke, tumour (e.g. medulloblastoma), alcohol, developmental (e.g. Arnold-Chiari malformation), non-metastatic paramalignant syndrome, trauma.

Clinical types

Benign essential (familial) tremor – Characteristically seen in the hands and sometimes the head and often precipitated by using the hands. It is frequently familial and aggravated by anxiety, tiredness, anger, fear. Alcohol may briefly alleviate the tremor. Drug therapy with propranolol or primidone may help.

Cerebellar tremor – (a) *Static tremor* – develops, if patient attempts to maintain a limb in a fixed posture. (b) *Action or intention tremor* – A disorder of co-ordination becomes evident in the distal part of the limb approaching its objective, e.g. in the finger nose test when there is a marked terminal wabble as the finger nears its object. Most frequently seen in multiple sclerosis.

Table 27: Classification of tremors

(a) *Rest tremors* – 3 to 6 Hz, with patient sitting or lying in repose.
(b) *Action tremor* – 8 to 10 Hz, while writing or pouring water.
(c) *Postural tremor* – 8 to 10 Hz, a type of action tremor with arms or legs.
(d) *Intention tremor* – A type of action tremor, bringing the finger to touch the nose.
(e) *Task-specific action tremor* – while writing only is primary writing tremor.
(f) *Orthostatic tremor* – 11 to 20 Hz, fast tremor while standing only. Responds to clonazepam.
(g) *Dystonic tremors* – Tremors associated with abnormal posturing (dystonia).
(h) *Rubral or midbrain tremors* – Combination of rest tremor worse with posture and action.
(i) *Slow tremors* – 1 to 3 Hz. Myorhythmia in brainstem pathologies, Whipple's disease.
(j) *Position specific tremor* – while holding a specific position like wing beating position.
(k) *Palatal tremor* – also referred to as palatal myoclonus resulting from lesions in Guillain-Mollaret triangle (formed by dentate nucleus, red nucleus, inferior olive via central tegmental tract).
(l) *Neuropathic tremor* – in HMSN, paraproteinemia associated neuropathies, reflex sympathetic dystrophy (usually postural tremors).
(m) *Fasciculatory tremor* – Irregular tremor caused by fasciculations of distal muscles across joints in MND and monomelic amyotrophy.
(n) *Cortical tremors* – A form of cortical myoclonus.
(o) *Psychogenic tremor* – Abrupt onset, spontaneous remission, various combinations of rest, postural and kinetic tremors, changing variable amplitude and frequency, increase with attention and less with distractibility, respond to placebo and psychotherapy.
(p) *Hereditary chin tremor* – AD inheritance.

Parkinsonian tremor – Usually begins in one upper limb and later involves lower limb on same side, the other side being affected in the same order after a further interval. Increased by emotional excitement and disappearing during sleep.

Flapping tremor (Asterixis) – detected at the wrists and fingers when the hands are outstretched. Seen in hepatic precoma, may occur in uraemia, barbiturate intoxication, CO_2 narcosis and respiratory failure.

Task-specific tremor – e.g. primary writing tremor, has the task specificity of dystonia, but the appearance of a localized essential tremor.

Orthostatic tremor – affects the legs and trunk and occurs only on standing still. The tremor may resemble essential tremor or be faster. It responds to clonazepam.

Wing beating tremor – A characteristic of Wilson's disease.

Pendular tremor (Red nucleus tremor) – Most violent form of tremor almost invariably seen in multiple sclerosis. Tremor often present at rest causing jerky extension movements of head, and inarticulate speech. Slightest attempt to move the arm is followed by severe wide amplitude tremor.

Neuropathic tremor – Tremor is unusual in peripheral neuropathy, but can occur in association with chronic relapsing inflammatory polyneuropathy, hereditary motor and sensory neuropathy and benign IgM paraproteinaemic neuropathy.

Searching movements – with eyes closed when afferent input is affected as in posterior column or parietal lobe lesion.

Infantile tremor syndrome – Rapid tremors usually affecting the whole body. Of unknown aetiology. An open mouth, vacant expression, light coloured sparse hair, pallor and puffiness of face may be other characteristics.

Hysterical tremor – A fine tremor localized to one limb or generalized, and a coarse irregular shaking intensified by involuntary movements.

5. **Tics:** are abnormal movements (motor tics) or abnormal sounds (phonic vocal tics). They can be simple or complex and occur abruptly. They are preceded by an inner urge (like akathisia) that is relieved by carrying out the movement. They are intermittent, repetitive, stereotypic. They can be voluntarily suppressed and are exacerbated with stress, boredom, fatigue. May persist in sleep:
   (a) Simple motor tics – Shoulder shrug, head jerk, blink, twitch of nose.
   (b) Complex motor tics – are coordinated patterns of sequential movements – touching the nose, kicking.
   (c) Simple phonic tics – Sniffing, throat clearing, grunting, coughing, sucking sounds.
   (d) Complex phonic tics – Shouting obscenities, profanities (coprolalia), repeating someone else's words (echolalia).

Causes – (i) Primary like Tourette syndrome, adult onset ticks, primary dystonia, HD, WD, neuroacanthocytosis. (ii) Secondary – encephalitis, drugs, e.g. levodopa, carbamazepine, phenytoin, dopamine blocking drugs. Toxins like CO. Mental retardation, Down syndrome, fragile X syndrome, head injury, stroke.

Writer's cramp – is a task specific focal dystonia usually of adult onset or childhood onset.

LOCALIZED INVOLUNTARY MOVEMENTS

Involuntary Movements of Face and Neck

1. ***Spasmodic torticollis*** – Tonic or tonic-clonic movements resulting in deviation of head to same particular direction.
   Causes – Lenticular disease, arthritis of cervical joints, painful tooth, glandular swelling, acute dystonic reaction to neuroleptic drugs, or idiopathic.
   Treatment – Anticholinergic drug may help. In some cases injection of botulinum toxin, or surgical division of spinal accessory nerve and upper cervical posterior primary rami may help.
2. ***Titubation*** – A vertical oscillation of the head seen when patient sits up or stands and disappearing on lying down. Causes – Disease of cerebellar connections, most commonly seen in multiple sclerosis, old age.
3. ***Hemifacial spasms*** – Twitching of muscles supplied by the facial nerve, usually a sporadic disease, clonic, tonic or paroxysm of clonic. MRI may show a vascular loop compressing the facial nerve root entry zone. Demyelination of facial nerve. A condition of varied aetiology in adults manifesting itself by clonic spasms of facial muscles and platysma on one side of face. Degree of affliction varies from slight and occasional twitching around mouth or eye to a constant severe spasm which screws up the eye and distorts angle of mouth. Spasm is both precipitated and exaggerated by excitement and tension.

Movements Limited to Muscles

1. ***Fasciculations*** – Visible spontaneous contractions of groups of muscle fibres supplied by a single anterior horn cell (single motor unit) indicate degeneration of anterior horn cells, or irritation of the anterior root. (Produced by denervation hyper-sensitivity to existing acetyl choline.) Table 28 lists the causes of fasciculations.
2. ***Myokimia*** – (a) Fine, rapid rippling of muscle fibres most commonly seen in orbicularis oculi usually due to fatigue, common in psychoneurosis. (b) Coarser contraction of bundles of muscle fibres both visible and palpable commonly in outer aspect of thigh, arms, pectorals and intercostals, common in fatigue and neurasthenic states. (c) Facial myokimia – Continuous movements likened to a 'writhing bag of worms'. The condition may occur in attacks and is usually associated with structural disease of the brainstem (pontine glioma) in particular with multiple sclerosis and intrinsic brainstem tumour, or in Guillain-Barre syndrome.

Table 28: Causes of fasciculations

- Benign or physiological following exertion
- Anterior horn cell diseases
  - Motor neuron disease
  - Syringomyelia
  - Hereditary spinal muscular atrophies
  - Acute phase of poliomyelitis
  - Spinal cord tumour or ischemia.
- Poisoning
  - Organophosphorus poisoning
  - Nerve agent exposure

3. ***Writer's cramp*** (Craft) – A specific complaint of inability to write (or type) may occur as a presenting feature of a psychological disturbance or a variety of diseases such as joint disease, carpal tunnel syndrome, Parkinson's disease, spastic or ataxic hand, benign essential tremor and torsion dystonia. Task specific dystonia.
4. ***Focal dystonia*** – Dystonia, particularly when it begins in adult life, often takes the form of a localised involuntary movement affecting one part of the body.
5. ***Flexor-extensor spasms*** – in paraplegic patients.
6. ***Blepharospasm*** – Intermittent spasms of contraction of orbicularis oculi sometimes seen in Parkinson's disease or torsion dystonia, or provoked by neuroleptic drugs. May occur as isolated phenomenon and without apparent cause in middle-aged or elderly patients. It is a focal dystonia.
7. ***Orofacial dyskinesia*** – Spontaneous movements of mouth, lips and tongue in elderly and chronic psychiatric patients. Most commonly seen as a result of prolonged treatment with neuroleptic drugs. May occur in Huntington's chorea or torsion dystonia, or rarely spontaneously (levodopa therapy).
8. ***Palatal myoclonus*** – Regular, rhythmic contraction of soft palate, causing the uvula to bob up and down, and speech to be tremulous. Usually appears acutely following vascular lesion in region of red nucleus, olive or dentate nucleus; may occur with tumours in the same region.
9. ***Shivering*** – Rapid regular movement of the whole muscle due to cold or nervousness.
10. ***Akathisia*** – is a state of extreme restlessness with and inner urge to move about and is seen most often as a side effect of neuroleptic drugs, i.e. as a symptom of tardive dyskinesia.
11. ***Startle*** – is a natural defensive reaction, which may be excessive in some families and insuppressible (hyperreflexia). It is also a prominent feature, with myoclonus, of the spongiform encephalopathies.

Drug-induced involuntary movements – (i) *Tremor* – bronchodilators, tricyclics, valproate, lithium. (ii) *Pseudoparkinsonism* – Phenothiazines, butyrophenones like haloperidol, reserpine, tetrabenazine. (iii) *Acute dystonias* – Phenothiazines, butyrophenones, metoclopramide, diazoxide. (iv) *Akathisia* (inability to sit still) – Phenothiazines, butyrophenones. (v) *Tardive dyskinesia* –Phenothiazines, butyrophenones.

9. GAITS

DIAGNOSTIC IMPORTANCE IN NEUROLOGY

Unilateral Defect

1. *Hemiplegic (circumduction) gait* – Active forward projection of paralysed limb difficult; front of foot, especially the lateral part of the sole against the ground.
2. *Unilateral high-stepping gait* – of flaccid type in compression of external popliteal nerve or damaged anterior horn cells as in polio. Hip and knee lifted too high in order to clear the drop foot from the ground, and brought loosely down.
3. *Limping gait* (Antalgic gait) – in sciatica. Patient limps with short steps, keeping the painful limb semiflexed and dropping the pelvis, towards the painful side.
4. *Hysterical gait.* (i) *Forward gait* – unilateral dragging gait with scraping of the inner border of the foot, as opposed to the outer border in organic hemiplegia; or the whole foot is dragged along the ground. (ii) *Side gait* – In hysterical hemiplegia, side gait impaired on both sides. In organic hemiplegia the patient moves sideway towards the paralysed side well, but badly towards the healthy side.

Bilateral Defect

1. *Spastic gait* – In spastic paraplegia patient moves swiftly along with abnormally short steps, the front part of the foot clinging to the ground, produced by bilateral circumduction of the legs. In severe cases, tendency to ankle clonus causes a trepidation of the whole body from tremors of the feet.
2. *Scissor gait* – A form of spastic gait with legs crossing alternately in front of each other, producing the cross-legged or "Scissor" gait in congenital cerebral diplegia.

3. *Ataxic gait* – (a) *Cerebellar* – Gait is of two types – (i) Ataxia of legs (Reeling gait). Broad based, walks like a drunkard – The patient tends to reel in several sideways steps towards the side of lesion. (ii) Ataxia of trunk – Patient is grossly unstable and reels in any direction. This is seen in midline posterior fossa lesion including tumours of vermis and foramen magnum abnormalities. (b) *Titubant ataxia* – Ataxia with vertical oscillation of head, trunk and arm in multiple sclerosis.
4. *Reeling or tottering gait* – in severe vertigo, diplopia or alcoholic intoxication. Unsteadiness especially marked on sudden turning.
5. *Vestibular gait* – Tilts to same side when walking forwards and to the opposite side when walking backwards.
6. *Bilateral high steppage (equine) gait* – Patient lifts the leg too high flinging the ankle up (slapping gait) due to foot drop. This type of gait when bilateral is seen in polyneuritis, muscular dystrophies, peroneal muscular atrophy and sometimes lesions of cauda equina.
7. *Stamping gait* – seen in tabes dorsalis where the patient walks on a broad base, lifts the legs unduly suddenly and violently, raising them too high and then bringing them down forcibly stamping the heels on the ground (stamping gait). May also occur in carcinomatous neuromyopathy or compressive lesions of posterior columns.
8. *Festinant or shuffling gait* – (Small step gait). Movement in a series of small shuffles either due to rigidity of extrapyramidal disease or combined rigidity, instability and lack of confidence in cerebral arteriosclerosis.
9. *Waddling or duck-like gait (myopathic gait)* – The pelvis is rotated through an abnormally large arc, accompanied by compensatory movements of the upper trunk and associated with marked lordosis. Usual causes are progressive muscular dystrophy and other myopathies, chronic forms of spinal muscular atrophy and congenital dislocation of the hips.
10. *Jaunting gait* – in chorea. Sometimes one foot seems to be momentarily entangled by an invisible obstacle which holds the child back for an instant, or his knee may give way suddenly causing him to fall.
11. *Toppling gait* – is characterised by tottering and sudden lurches, resulting in a hesitant and uncertain gait and unexpected falls, in the absence of weakness, ataxia, or loss of deep sensation. It is observed in progressive supranuclear palsy, advanced stages of Parkinson's disease and some cases of inferior cerebellar infarction (toppling to one side only).
12. *Frontal lobe disorders of gait* – Posture is fixed, the base somewhat widened, the gait slow, steps small, marches at the place (slipping clutch sign), hesitant and eventually shuffling (*marche de petit pas, magnetic foot*). Seen in diffuse cerebrovascular disease. Final stages are associated with dementia, oppositional resistance (*genenhalten*) and rigid flexed posture (cerebral paraplegia in flexion).
13. *Gait of normal pressure hydrocephalus* – In absence of significant weakness, tremor, rigidity or ataxia, the base becomes widened, the gait is slowed, the height and length of each step are diminished, with a tendency to shuffle. Difficulty with initiation of gait and tendency to fall backwards are late signs.
14. *Hysterical gait* – A bizarre gait not resembling any known pattern of organic disease. Absence of neurological signs.
15. *Spastic springing gait* – In lathyrism – at first patient walks on tip toe, the body is raised high before the toes leave the ground, giving rise to up and down movements of the shoulder, and progression is effected by tilting the pelvis and circumducting the legs. The legs are crossed scissorwise. Later patient uses one or two long sticks.
16. *"Frog" like gait* – In later stages of muscular dystrophy when the power of standing erect is lost. The patient crawls on hands and toes.
17. *Violent contortions* – of spinal column when walking in torsion dystonia.
18. *Transient dyscrasias* – e.g. intermittent arterial claudication. Normal walk at start, but after going some distance, patient stands still or sits down to rest till the spasm relaxes and then starts off again.
19. *Gait in myotonia congenita* – As soon as the patient starts to walk, the first steps are like those of a man dragging out of a deep mud-hole but as the patient perseveres, the muscles become active and the gait normal.
20. *Dromedary or camel back gait* – with protrusion of buttocks in facioscapulohumeral dystrophy.
21. *Toe-walking gait (Tip-toe gait)* – Tight heel cords limit dorsiflexion of the foot makes patient stride on the balls of his feet, without a definite heel strike. Such a gait occurs in Duchenne's muscular dystrophy, dermatomyositis, in spastic diplegia and in autistic or retarded children.
22. *Nocturnal flipping hand gait* – In carpal tunnel syndrome, patient may get up in the night and walk about the room flipping or shaking his hand in an effort to gain some relief.

23. *Dancing bear gait* – The effort to walk after trying to rise from the chair, may result in stepping on the same spot, as if trying to free the feet, from sticky mud.
24. *Charlie Chaplin gait* - In homocystinuria most patients have to out gait, with bilateral hip flexion contractures patient adopts this gait with both buttocks prominent.

10. HEADACHE

CAUSES

I. Intracranial and local extracranial

1. *Trauma* – Contusional or post-traumatic headache.
2. *Intracranial inflammations* – Meningitis, encephalitis, cerebral abscess.
3. *Vascular headaches* – Hypertension, cerebral or subarachnoid haemorrhage, intracranial aneurysm, vasodilator drugs like nitrites and histamine, adrenaline. Menopausal. Alcohol hangover or withdrawal, coffee withdrawal. Giant cell arteritis (temporal arteritis), thrombosis of intracranial venous sinus.
4. *Traction headache* – Pain produced by intracranial arterial displacement and distortion of the dura, usually caused by space occupying lesions or raised intracranial pressure or low intracranial pressure (intracranial hypotension).
5. *Post-lumbar puncture headache* – Low CSF pressure headache.
6. *Cough headache* – A benign syndrome of severe headache which accompanies coughing, straining or sneezing can be due to posterior fossa tumour.

II. Cranial neuritis and neuralgias

Of sensory nerves of scalp, e.g. orbital neuralgia, or neuralgia of auriculotemporal, posterior auricular or great occipital nerves, herpes of Gasserian ganglion.

III. General or systemic causes

1. *Anoxaemia* – Anaemia, carbon monoxide or carbon dioxide poisoning.
2. *Toxic* – Fevers, uraemia, eclampsia, metallic poisoning, "alcoholic" hangover, post- convulsive, drugs like quinine, tobacco, cocaine, morphine, sulphonamides. Pelvic or gall bladder disease, constipation, intestinal stasis. Nervous exhaustion.
3. *Metabolic factors* – Hypoglycemia, alkalosis or acidosis.
4. *Haemopoietic factors* – Essential polycythemia, thromobasthenia.

IV. Referred pain

1. *Eyes* – Errors of refraction, glaucoma, iritis, etc.
2. *Ears* – Otitis, mastoiditis, vestibular nerve lesions, Eustachian tube block, tumours of middle and inner ear.
3. *Teeth* – impacted teeth, infected tooth sockets and dental roots.
4. *Paranasal sinuses* – Infection of paranasal sinuses may cause localised pain.
5. *Neck* – Diseases of upper cervical spine may be associated with both occipital and frontal pain.

V. Psychogenic

Common cause of headache in depression.

VI. Tension (muscle contraction) headache

Pain resulting from sustained contraction of skeletal muscles of the neck, frontalis, occipital muscles due to emotional tension.

VII. Exertional headache

Headache may come on during exertion and persist for few hours afterwards.

VIII. Other primary headaches

(i) Hypnic headache syndrome is a late onset disorder and usually wakes up the patient from sleep at around the same time every night. The headache is usually treatable with flunarizine and lithium.

(ii) Exploding head syndrome can occur any time during day or night.

INVESTIGATION OF A CASE OF HEADACHE

History

1. *Incidence* – Anxiety headaches, migraine, and those due to fevers, sinus disease and eyes most common.
2. *Age* – (a) *Children* (3–16 years) – Migraine, fatigue / psychogenic, post-traumatic, rarely tumour (post. fossa). (b) *Adults* (17–65 years) – Tension, migraine, cluster, post-traumatic, tumour/subdural hematoma. (c) *Elderly* (above 65) – cervicogenic, chronic tension, cranial arteritis, continuing migraine, tumour/subdural hematoma, glaucoma, cluster, Paget's disease of skull.
3. Onset and duration of headache –
   (i) *Acute headache* – Trauma, spontaneous intracranial hemorrhage, hydrocephalus, tonsillar impaction or acute meningeal irritation (SAH or meningitis). Acute tension headache or migraine.

Thunder clap headache – Acute severe intensity headache in SAH, reversible vasospasm.

(ii) *Recurrent or chronic headache* – Migraine, migraine plus tension headache (mixed headache) or daily continuous headache (tension headache), are the three common headache syndromes.

4. *Character* – (a) *Pulsating or throbbing* in fever, migraine and arterial hypertension. Sense of tightness or external pressure in brain tumour and meningitis. (b) *Most intense headache* usually in subarachnoid hemorrhage, migraine, fever, meningitis, hypertension, acute cerebral venous thrombosis and terminal phase of brain tumour. (c) *Paroxysmal* in neuralgia. (d) *Psychogenic headache* is often described in over-elaborate terms. (e) *Pain with intracranial tumour* is usually deep, nonthrobbing, dull aching, on waking up, intermittent and lasts from few minutes to hours. (f) *Tension headache* usually bilateral and described as band or cap-like pressure, or constant headache with sharp jabs of pain. Pain usually worse in evenings. (g) *Traction headache* has a bursting quality, typically wakes the patient but disappears soon after rising. (h) *Headache of raised ICP* – Dull ache, worse in morning, worse on coughing, straining, bending. (i) *Cluster headache* - pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating and explosive in quality. A core feature of cluster headache is periodicity (j) *Paroxysmal hemicrania (PH)* is characterized by frequent unilateral, severe short-lasting episodes of headache. (k) *Short lasting unilateral neurologic headache attacks syndrome* has manifestations of an overlap between cluster headaches and trigeminal neuralgias. (l) *Drug - rebound headache* when offending drug is withdrawn, the prophylactics which were not effective start working and frequency of headaches comes down.
5. *Site and distribution* – Pain with local distribution suggests organic cause. Psychogenic headache usually diffuse, though first evident in neck and occiput. Headaches due to hypertension, cerebral tumour, toxic, infective and reflex headaches also usually diffuse. A unilateral headache in one or other temple may be due to temporal arteritis or intracranial causes such as inflammation or compression. Sinus headache in front of head at onset. Headache bizarre in quality and varying in location usually of psychogenic origin. Posterior headaches extending into the nuchal region or even the shoulder muscles are almost always due to muscle tension.
6. *Provoking and aggravating causes* – Migraine made worse by assuming horizontal position or by jolting. Lying down position may at first make the headache of sinusitis more intense but subsequently it subsides. Sudden change of position or head jolt may aggravate headache of intracranial tumour. Muscle contraction headache usually reduced by movements of head and neck. Psychogenic headache likely to be increased by emotional stress and mental fatigue. Vascular or inflammatory headaches of intracranial origin are accentuated by coughing or other forms of brief straining.
7. *Associated symptoms* – (a) *Nausea, anorexia and vomiting* most common in migraine, vomiting without nausea in brain tumours. (b) *No vomits* in headache of sinus or eye disease. (c) *Visual disturbances* usually precede headache in migraine. When visual defects outlast the headache, likelihood of cerebral vascular accident or brain tumour. (d) *Depression or anxiety* in psychic headache. (e) *Symptoms of nasal obstruction,* or discharge, or pharyngeal discharge in sinusitis. (f) *With facial pain syndromes* – Tension headache, migraine, raised intracranial pressure, benign paroxysmal headache, trigeminal neuralgia, atypical facial pain, post-herpetic neuralgia. Visual obscuration in elevated intracranial pressure.
8. *Sleep* – Long periods of insomnia because of headache most likely due to anxiety. Meningeal headaches may produce loss of sleep.
9. *Family history* – of migraine.

Physical Examination

1. Of the whole body including neurologic examination.
2. Tenderness – of muscles of head and neck in myositis, of scalp in tension headache. Muscle spasm in meningitis. Local tenderness at site of periostitis of bone. Tenderness of scalp after head injuries. Tenderness over temporal arteries in temporal arteritis.
3. Palpation of skull – may reveal the engorged and strongly pulsatile scalp artery of a migraine headache or tenderness and localised erythema of temporal or other cranial arteries.
4. Blood pressure – Accelerated hypertension.
5. Auscultation of mastoid region, and of eyes with the lids gently closed for a bruit.
6. Fundus examination – Papilloedema.
7. Examination of sinuses – Sinus tenderness.

Psychiatric Evaluation

For depression, repressed hostility, aberrant personality problems, most patients with emotion-induced headache.

IV. Investigations

1. X-rays – (a) Of paranasal sinuses. (b) Of skull for evidence of increased intracranial tension or pineal shift. (c) Of cervical spine – for cervical spondylosis.
2. CSF – for evidence of meningitis, cerebral abscess or subarachnoid hemorrhage. CSF pressure manometry for pseudotumour cerebri.
3. Complete blood count – Leucocytosis in meningitis, sinusitis, cerebral abscess. Evidence of anaemia, dyscrasias, leukaemia.
4. Serological tests – for neurosyphilis.
5. Urine – Chronic urinary infection.
6. Fasting blood sugar – Hypoglycemia.
7. Serum creatinine – Uraemia.
8. ESR – Raised in temporal arteritis and infections.
9. EEG – High incidence of abnormality in patients with vascular headaches.
10. CT scan – for diagnosis of intracranial tumours especially fast growing neoplasms such as pituitary tumours, acoustic neuroma, craniopharyngioma.
11. Cerebral angiography – for tumour, berry aneurysm or angiomatous malformation.
12. MRI – is particularly useful for delineating and identifying tumours at the base of the skull, and for demonstrating metastatic lesions. Magnetic resonance imaging is more sensitive in the brain than CT scan, but sometimes less specific.
13. MRV – for venous sinus thrombosis.

Biopsy of Affected Artery

(usually temporal) in giant cell arteritis.

Response to Treatment

Tension headache may be relieved with tranquillizers or infiltration with 10 to 20 mL. One percent procaine solution, if localised areas of tenderness can be outlined. Sumatriptan relieves migraine. Sinus puncture or antibiotics relieve headache of sinusitis.

MIGRAINE

Recurrent attacks of headache, varied in intensity, frequency and duration; commonly unilateral in onset, and usually associated with anorexia and sometimes with nausea and vomiting. Some are associated with conspicuous sensory, motor and mood disturbances.

Aetiology

(i) *Age* – The onset may be in childhood with cyclical vomiting; typical migraine appears in adolescence and continues at intervals until the sixth decade, when the attacks may cease apart from occasional teichopsias. (ii) *Sex* – More common in women. (iii) *Hereditary influences* – the transmitted factor being an abnormal response of cranial and other vasculature to certain external or endogenous stimuli. (iv) *Precipitating causes* – Prolonged fasting, prolonged exposure to bright light. Particular foods, especially cheese, chocolates, citrus fruits, bananas, coffee. Mild associated head injury, e.g. heading a football. Changes in the degree of stress. (v) *Conditions associated with migraine* – Tension headache, the periodic syndrome (recurrent bilious attacks of childhood), epilepsy, allergy.

Mechanisms: Familial tendency towards enhanced vascular contractility in migraine patients produces a sequence of constriction and dilatation. Stimuli which normally produce a healthy flush may produce an incoordinated circulatory response in migraine patients resulting in constriction of small vessels and dilatation of arteries and veins. Serotonin released from platelets produces vasoconstriction. Serotonin then gets adsorbed into vessel wall and in combination with locally released heparin and neurokinin produces pain. Fall of plasma serotonin results in overaction of dilator substances like histamine, bradykinin and prostaglandin E. Serotonin release from platelets is increased by free fatty acids and IgG aggregate.

Classical Migraine

Prodrome – Vague, yawning, euphoria, excessive energy or depression and lethargy.

Aura – usually visual. Flashing lights, zigzag castellations, balls or filaments of light may start peripherally and centrally. Fragmentation, jigsaw appearance (teichopsia), with or without central scotomata, micropsia and metamorphosia are common. The aura typically lasts half hour and is succeeded by headache.

Headache – May be hemicranial or soon becomes generalised. Starts as vague pain and builds up to a throbbing intensity, over the temporal or frontal region associated with pallor, anorexia, nausea, vomiting and photophobia. It may last for several hours and after vomiting has occurred, may decrease in intensity and be followed by sleep. In some headache persists for 48 hours or more. During the headache the superficial temporal artery may be congested and pulsating.

Simplified Diagnostic Criteria for Migraine

Repeated attacks of headaches lasting 4–72 hours that have features listed in Table 29.

Migraine Variants

Common migraine – More common than classical migraine, it is less often unilateral and not preceded by aura. Attacks are more often related to factors such as menstruation and relaxation after stress.

Vertebrobasilar migraine – Due to spasm of vertebrobasilar artery. Usually starts in third decade and differs in symptomatology from classical migraine – Aura may include ataxia, bilateral paraesthesiae, vertigo, diplopia or even transient loss of consciousness. Headache is commonly occipital.

Hemiplegic migraine – Often familial. Headache is followed by contralateral hemiparesis or hemiplegia which may last up to 10 days. Patient may have several attacks affecting one side of the body, whereas the next attacks may affect the opposite side.

Migrainous neuralgia (Cluster headache) – occur mainly in men. (i) *Episodic* – (a) Severe unilateral supraorbital and/or temporal pain lasting 15–180 minutes, if untreated. (b) Headache associated with at least one of the following on the painful side namely conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial flushing, miosis, ptosis, eyelid oedema. (c) Incidence of attacks range from one attack on alternate days to eight attacks/day. (ii) *Chronic* – Attacks occur for more than one year without remission, or with remission lasting less than 14 days. Occur in clusters with headache free period.

Treatment – Oral or rectal ergotamine 1–2 mg should be given at onset of headache. Not more than 12 mg/week, or sumatriptan 100 mg p.o. or 6 mg s.c. given in anticipation of attack; or with methysergide 1–2 mg t.d.s. or verapamil 40–80 mg t.d.s., for the duration of cluster. Oxygen 6-8 litres/min, often affords relief within 10 mins. In more refractory cases Prednisolone 40 mg/day reducing over 3–6 weeks and lithium carbonate 250–1500 mg/day may be beneficial.

Table 29: Criteria for migraine

A. Normal physical examination
B. No other reasonable cause for the headache
C. At least two of:
– Unilateral pain
– Throbbing pain
– Aggravation of pain by movement
– Moderate or severe intensity
D. At least one of:
– Nausea or vomiting
– Photophobia and phonophobia

Post-traumatic migraine – A minor head injury or heading the ball in soccer players (footballer's migraine) may result in a migrainous type of headache, accompanied by vertigo and occasionally vomiting.

Ophthalmoplegic migraine – Headache is commonly around the eye and is accompanied by weakness of movement of one eye (usually III nerve) which may outlast the headache by some days. Children are more commonly affected.

Facial migraine – Unilateral episodic facial pain associated with symptoms suggestive of either migraine or cluster headache. It can be distinguished from migrainous neuralgia by longer duration of pain, lack of clustering, and more frequent episodes of nausea and vomiting.

Abdominal migraine – typically occurs in children, paroxysmal mid-abdominal pain with nausea and vomiting, flushing or pallor.

Retinal migraine – Loss of vision limited to one eye.

Complicated migraine – Patient is left with a persistent neurological deficit after a migraine attack. This occurs most commonly after hemiplegic migraine. CT scan has revealed this to be a much more common occurrence than previously believed, and the pathological basis is presumably infarction after ischemia.

Symptomatic migraine – The term is used when symptoms suggest diagnosis of migraine but where a structural lesion is found such as angiomatous malformation usually in occipital lobe.

Vestibular migraine – Migraine can present with vertigo.

Childhood migraine – Children with migraine may present with transient neurologic, autonomic, GI or visual symptoms and headache may not be the primary symptom. The duration is short. Pain may be unilateral or bilateral (bifrontal or bitemporal).

Menstrual migraine – develops must frequently in the second decade of life and can be a part of premenstrual syndrome usually without aura, and resolves with onset of menstruation.

Migraine equivalents – Prodromal symptoms occur without headache or vomiting.

Management

During Attack

1. *Analgesics* – NSAIDs, e.g. diclofenac can be given p.o. or i.m. and is particularly useful when severe vomiting is a feature.

   Sublingual Piroxicam has significant analgesic effects in acute migraine without aura with excellent tolerability

2. *Ergotamine* – (a) Ergotamine tartrate 0.25 to 0.5 mg i.m. or orally 1–2 mg. tablet preferably in combination with 100 mg caffeine – 2 tablets at onset followed by 1 tablet after 30 minutes, if necessary, or (b) Dihydroergotamine 1 mg i.m., or 1–2 mg by mouth. Whichever preparation is used, a high dose often causes nausea and vomiting. These may be prevented by giving cyclizine 50 mg. or chlorpromazine 25 mg Contraindications to ergotamine – Septic or infectious states, peripheral vascular disease, coronary disease, pregnancy, thyrotoxicosis.

3. *5-HT_1 agonists* – are thought to modulate central pain mechanisms by reducing levels of the transmitter substance calcitonin gene related peptide.

   Sumatriptan 6 mg s.c. gives relief from headache in 60 minutes, with corresponding improvement in nausea, vomiting and photophobia. Oral dose of 100 mg provides relief within 2 hours. Headaches recur within 48 hrs in little less than half the patients. Contraindications – IHD, Prinzmetal's angina and arrhythmias.

   Rizatriptan given orally acts faster than sumatriptan. Rizatriptan wafers may be helpful in cases of nausea with migraine, as they can be taken without fluids, reducing the likelihood of vomiting. Side effects include chest pain and paraesthesia. Naratirptan 1mg or 2.5 mg has less rebound and is more effective.

   Zolmitriptan nasal spray 5 mg gives relief in 5 minutes.

4. *General* – Lying in a darkened and quiet room and ice pack to the head may help.

Reducing Frequency and Severity of Subsequent Attacks

1. Elimination of trigger factors – e.g. Sleeping late, irregular and hurried meals, certain foods, especially chocolate and fried food, or missing of meals, psychological stress, contraceptive pills. Treatment of cervical spondylosis.
2. Relaxation exercises – which may include biofeedback from a temporalis electromyogram. Yoga, Pranayama.
3. Drugs:
   (a) *Serotonin (5-HT) inhibitors* – (i) *Calcium antagonists* – such as Flunarizine 10 mg/day (ii) *Cyproheptadine* 4 mg t.d.s. (can cause sedation and wt. gain). (iii) *Pizotifen* 0.5 mg t.d.s. or 1.5 mg nocte. (iv) *Methysergide* 1–2 mg t.d.s. is the most effective drug in this group but should be used under supervision in courses not exceeding 3–4 months. Pleural, pericardial and retroperitoneal fibrosis are serious side effects.

   (b) *Topiramate* – an antiepileptic drug used in prophylaxis of migraine, Dose: 2.5 to 5 mg b.d. Side effects – Paraesthesia, renal calculi and wt. loss, fatigue, anorexia.

   (c) *Divalproex (valproic acid)* 200 mg b.d. Side effects - weight gain, tremor, hepatotoxicity.

   (d) *Tricyclic agents* – e.g. Amitryptiline 25 mg tds may be effective irrespective of the presence of depression.

   (e) *Ergotamine tartrate* – for histamine cephalgia 1 mg. by mouth or 0.25 mg by self-administered injection or by suppository used regularly last thing at night can be continued for many weeks without harmful effects, 2 days being left without treatment each week.

   (f) *Hormones* – Progesterone given for last eight days may be useful for migraine occurring in the immediate premenstrual period or at beginning of catamenia. When migraine begins or becomes worse at the time of menopause, oestrin, given in small doses as continuous therapy sometimes helpful.

   (g) *Schedule* - (a) Propranolol 40–160 mg/day or flunarizine 5–10 mg/day as first line of therapy. (b) In patients with episodic and chronic migraine Topiramate 50–100 mg/day. (c) In patients with episodic migraine Divalproex 250–750 mg/day (d) For mixed migraine and tension type headache - Amitryptiline 10–25 mg/day. After 6–12 months of prophylaxis gradual withdrawal should be considered.

11. EPILEPSY

Epilepsy – It is a tendency for recurrent unprovoked seizures, usually two or more seizures. Characterized by recurrent episodes primarily of cerebral origin, in which there is a disturbance of movement, sensation, behaviour or consciousness. These episodes begin suddenly and have a tendency to disappear spontaneously.

Causes: Almost all disorders involving the grey matter can cause epilepsy.

Type of seizure – An epileptic seizure is an abnormal paroxysmal discharge of cerebral neurons sufficient to cause events that are apparent to the subject, an observer or both.

- Partial seizures begin locally in the cortex. Such seizures may spread and become generalized, involving the whole of the cortex.
- Generalized seizures in contrast, involve much of the cortex bilaterally from the outset, and always cause immediate loss of consciousness.

GENERALIZED SEIZURES

Generalized tonic-clonic seizure, following a partial seizure or occurring spontaneously, may be heralded by a cry, followed by loss of consciousness, falling to the ground with spasm of the limbs and deepening cyanosis in the tonic phase; the subsequent clonic phase is marked by stertorous breathing, and jerky limb convulsions of increasing amplitude and decreasing frequency. The tongue may be bitten. Incontinence of urine and faeces may occur. The seizure is typically followed by coma with an ascending consciousness level, then by confusion, headache, aching limbs and a desire to sleep, before complete recovery.

Epileptic myoclonic jerks (usually a sudden flexion movement of the arms) are also generalized seizures and occur in various syndromes. They are usually not associated with loss of consciousness, unless accompanied by absences.

Absences are generalized seizures, and may be simply a sudden brief cessation or slowing of activity, with rapid return to normality without loss of posture. It manifests as subtle motor activities like rapid blinking, chewing mvements or movement of hands. Typical absences are accompanied by characteristic 3 Hz spike-and-wave EEG activity. Atypical absences show slower or poorly formed spike-wave EEG activity (frequency ≤ 2.5 Hz); they may be more prolonged than typical absences.

Atonic seizures **–** characterized by sudden loss of postural muscle tone with brief loss of consciousness without postictal confusion.

Partial seizures (Focal seizures) – Occur in wide variety of forms. Consciousness is not impaired in simple partial seizures. Complex partial seizures are defined by impairment of consciousness, which may occur from the outset or may evolve from a simple partial seizure, automatism may also occur.

Temporal lobe seizures – are partial complex seizures associated with abnormal experiences of smell or feelings of unreality (jamais vu) or undue familiarity (déjà vu). Visual hallucinations may be seen and absence attacks or vertigo or rising epigastric sensation may occur.

Automatisms (semi-purposeful release phenomena) can occur in complex partial seizures or prolonged absences. Clinical features include lip-smacking, swallowing, fidgeting with the hands and more complex behaviours including vocalization, speech and wandering.

Status epilepticus – Recurrent seizures without gap of consciousness. The duration is usually 60–120 secs. Seizures lasting more than 30 minutes is established status. Treatment should be initiated, if seizures lasts more than 5 min (early status).

Any seizure type may occur, usually in patients known to have epilepsy.

- Generalized tonic-clonic status epilepticus is the most dramatic; the most common causes are anti-epileptic drug withdrawal or non-compliance, meningitis, encephalitis (Figs. 11 and 12) or abscess (particularly frontal) and alcohol withdrawal.
- Complex partial status epilepticus may manifest with prolonged periods of confusion and disorientation, associated with automatic activity for which there is amnesia.
- Absence status epilepticus often occurs in the context of learning disability or *de novo* in older individuals, and may be associated with confusion, disorientation or cognitive slowing.
- Epilepsia partialis continua is focal (usually motor) status epilepticus, often reflects underlying structural abnormalities, and may be unremitting for months or years despite treatment with anti-epileptic drugs. (Rasmussen's encephalitis).

Table 30 gives classification of epilepsy (abbreviated ILAE).

DIAGNOSIS OF EPILEPSY

1. **History**– *(a) Age of onset* – (i) Infancy – Metabolic disturbance associated with febrile illness, birth asphyxia, congenital diplegia, congenital hemiplegia and cerebral damage resulting from birth injury. Occasional sequel of meningitis. Rare degenerative disease such as amaurotic family idiocy. (ii) Early childhood – Any of the congenital or acquired lesions above mentioned. Idiopathic epilepsy, encephalitis. (iii) Late childhood and adolescence – Idiopathic, following previous

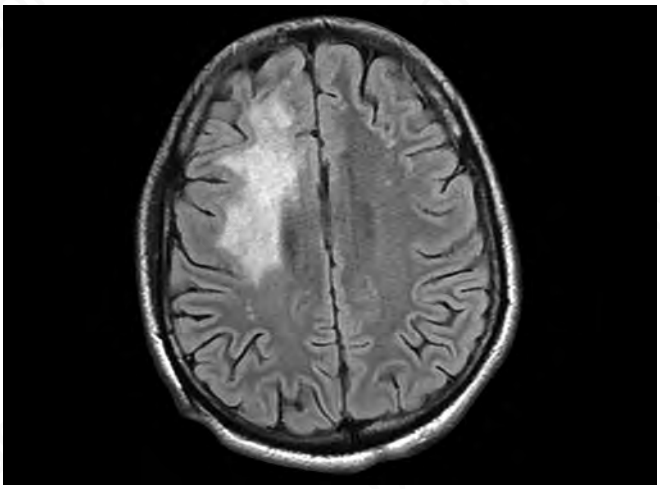


Fig. 11: MRI axial Flair image showing hyperintensity in white matter of corona radiata in a case of focal encephalitic

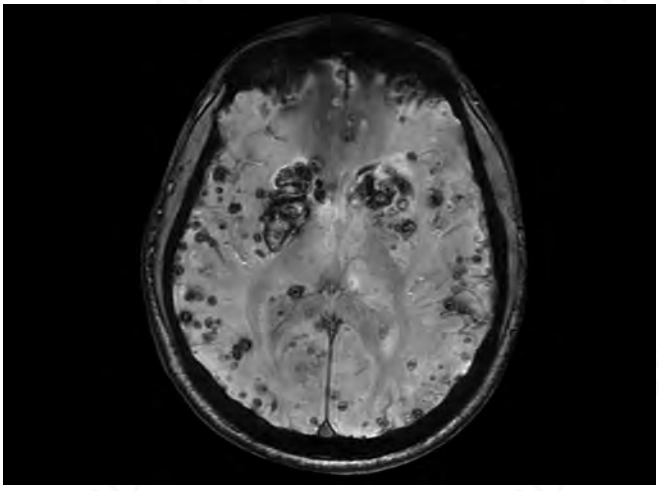


Fig. 12: MRI SWI shows multiple foci of blooming suggestive of hemorrhages in hemorrhagic encephalitis

Table 30: Classification of epilepsy (abbreviated ILAE) generalized epilepsies and syndromes

Idiopathic with age-related onset
• Benign neonatal familial convulsions
• Benign neonatal convulsions
• Benign neonatal epilepsy in infancy
• Childhood absence epilepsy
• Juvenile myoclonic epilepsy
• Epilepsy with generalized tonic-clonic seizures on awakening
Symptomatic or cryptogenic
• West syndrome
• Lennox-Gastaut syndrome
• Epilepsy with myoclonic-astatic seizures
• Epilepsy with myoclonic absences
Symptomatic
• Early myoclonic encephalopathy
• Early infantile myoclonic epilepsy with burst suppression
• Others
Localization-related epilepsies and syndromes
Idiopathic with age-related onset
• Benign childhood epilepsy with centrotemporal spikes
• Childhood epilepsy with occipital paroxysms
• Primary reading epilepsy
Symptomatic
• Epilepsy with simple partial, complex partial or secondarily generalized seizures arising from frontal, parietal, temporal or occipital lobes, or of unknown lobe of onset
Contd...

Contd...

• Epilepsia partialis continua
• Syndromes characterized by specific modes of activation
Unknown whether idiopathic or symptomatic
Epilepsies and syndromes undetermined (focal or generalized)
• Severe myoclonic epilepsy in infancy
• Epilepsy with continuous spike-and-wave activity in sleep
• Acquired epileptic aphasia
Special syndromes

trauma, infections. (iv) Adult life – Idiopathic epilepsy rarely begins after age of 25. Penetrating head injury involving meninges, intracranial tumour, cysticercosis. (v) Later life – Epilepsy most often due to cerebral arteriosclerosis. (b) *Aura or other prodromata* – and sensations experienced before attack. (c) *Description of fit from witness or family.* (d) *Circumstances under which fit occurs.* (e) *Associated features* – such as mental retardation. (f) *Family history* – Fits which cause sudden loss of consciousness with falling, followed by some confusion should be classified as grand mal. (g) *History of febrile convulsions in childhood.*

2. **Examination –** Presence of neurological signs (e.g. hemiparesis, dysphasia, field defect, may lateralize or localize a structural lesion. Dysmorphism and learning disability may suggest a chromosomal disorder, and progressive features (e.g. dementia, ataxia, worsening myoclonus) suggest a neurodegenerative disease. Cutaneous stigmata of the neurocutaneous disorder must be sought. A cardiovascular examination is

essential. The pupils may dilate during a seizure; other features may help lateralize the focus (dysphasia indicates dominant hemisphere onset, and unilateral automatisms are ipsilateral and unilateral dystonia contralateral to a temporal lobe focus).

3. **Investigations** –

Confirming the diagnosis:

EEG – is of value in establishing the diagnosis of epilepsy and an aid in determining the type of seizure. (a) Normal – Series of small alpha waves about 10 per second and occasionally smaller beta waves. (b) During attack an abnormal rhythm develops – (i) Idiopathic generalized epilepsy – Generalized 3 Hz spikes/wave. Grand mal and Jacksonian epileptic attacks – series of sharp spikes. (ii) Absences –alternating large dome-shaped waves and sharp spikes (dart and dome rhythm). (c) Between the attacks 3 Hz5w interictal epileptiform activity – Abnormal in about 50%. Intermittent irregular slow waves especially in grand mal. Normal EEG does not rule out epilepsy.

EEG telemetry – in the form of ambulatory recording or videotelemetry, may be necessary, if diagnosis is in doubt despite apparently frequent seizures. If necessary presurgical investigations (e.g. intracarotid sodium amytal testing to determine lateralized memory function and language dominance, intracranial EEG to determine the seizure focus).

Further investigations – may be necessary. Hypoglycemia needs to be ruled out, particularly in patients with early morning seizures. Echocardiography, ambulatory EEG, urinalysis for catecholamine metabolites and porphyrin determination may be required.

Investigating the cause: *MRI* provides reliable diagnosis of hippocampal sclerosis (demonstrated as loss of volume on a T_1-weighted volumetric sequence and increased signal on a T_2-weighted sequence), cortical dysgenesis and small lesions. It also detects foacl lesions like tumor, AV malformations, mesial temporal lobe sclerosis.

Non-epileptic attack disorder – Nonepileptic attacks commonly comprise either prolonged motionlessness with preserved background EEG rhythms, or prominent, often waxing and waning movements including asynchronous limb flinging, pelvic thrusting and opisthotonus. There is no hypoxia but salivation, incontinence and injury may occur. These patients usually have underlying psychological or psychiatric problems.

Diagnosis – (a) Prolactin levels rise immediately after generalized tonic-clonic seizures and some complex partial seizures, and return to baseline within 50 minutes. This does not occur after absence seizures. Serum prolactin levels do not generally rise significantly after non-epileptic attacks. (b) Ictal EEG monitoring does not show the typical changes that may precede or succeed epileptic seizures in nonepileptic seizures.

Differential diagnosis of epilepsy is given Table 31.

Table 34 gives factors which influence recurrence of seizures.

Table 31: Differential diagnosis of epilepsy

Hysterical fit (Pseudoseizures, Table 32)
Syncope (Table 33)
• Cardiac disorders
• Arrhythmias
• Aortic or mitral stenosis
• Cardiomyopathies
• Myxoma
Neurological
• Vertebrobasilar insufficiency
• Cataplexy-narcolepsy
• Basilar migraine
• Third ventricular cyst
• Meniere's disease
• Episodic ataxias
• Movement and sleep disorders
Metabolic or endocrine
• Hypoglycemia
• Pheochromocytoma
• Carcinoid syndrome
• Porphyria
Psychological or psychiatric
• Hyperventilation
• Panic attacks
• Non-epileptic attack disorder
• Episodic dyscontrol syndrome
• Malingering
• Munchausen's syndrome

MANAGEMENT

1. General hygiene and diet – Avoiding physical exertion, regular habits of eating and sleeping, adequate diet. Avoid alcohol.

Table 32: Hysterical fit (Pseudoseizures)

Hysterical fit	Epileptic fit
Induced by emotional excitement	Fairly constant periodicity
No incontinence	Incontinence common
Patient not hurt	Tongue biting. At times injury from fall
Usually in presence of people	Can occur anywhere
Movements spectacular. No clonic or tonic sequences	Tonic and clonic phases
Plantar response down going	Extensor plantar response
Corneal reflex present	Corneal reflexes absent during attack
Pupils remain unchanged	Pupils dilate
No turning of head and eyes, eyeballs roll upwards, if eyes forcibly opened	Conjugate deviation of head and eyes
Attacks may be prolonged to impress spectators	Attacks of short duration
Recovery after attack sudden	Gradual recovery
EEG – normal	EEG – epileptiform abnormalities

Table 33: Syncope

	Tonic-clonic seizure	*Vaso-vagal syncope*
Precipitant	Unusual	Emotional, painful or stressful event
Circumstances	Any	Usually upright posture, crowded or hot environment
Onset	Usually abrupt	Usually gradual with feeling of faintness, nausea, sweating, greying of vision
Motor phenomenon	Often characteristic tonic-clonic	Usually flaccid without movement
Skin colour	Pale or flushed	Pale
Breathing	Stertorous, foaming	Shallow
Incontinence	Common	Unusual
Tongue biting	Common	Unusual
Vomiting	Unusual	Common
Injury	Common	Unusual
Postictal	Drowsy, confused, headache, sleep	Rapid recovery
Duration of unconsciousness	Minutes	Seconds

Table 34: Factors which influence recurrence of seizures

- Cause of seizure
- Seizure type
- EEG findings
- Family history of seizures
- History of febrile seizure
- Todd's paresis (transient postictal focal defect)
- Abnormal neurological findings

2. Drugs – Principles: (i) Adequate therapy, aim being cessation of attacks. (ii) Dosage adjusted to particular patient, small initial doses. (iii) Combination of drugs, if necessary. (iv) Continuity of treatment. Abrupt discontinuation of drugs dangerous. (v) Drug should be continued for 2 years after the last fit.

Choice of drug – depends on seizure type. (a) In localization related epilepsy, first-line prophylactics are lamotrigine, carbamazepine (slow-release), oxcarbamazepine, levetiracetam. (b) In primary generalized, symptomatic generalized and unclassified epilepsies, initial therapy should be lamotrigine or valproate (broad spectrum agents). Valproic acid is useful in absences and benzodiazepines in myoclonic jerks. Patients with refractory generalized epilepsy may benefit from adjunctive treatment with topiramate or levetiracetam, zonisamide, clonazepam, pregabalin. Antiepileptic drugs are summarized in Table 35.

Plan of Management

(a) *Initial regimen* – The drug selected must be used in monotherapy. The drug should be introduced in small doses, since rapid introduction may cause side effects (particularly carbamazepine).

(b) *Maintenance treatment* – The aim should be to find the lowest dose which achieves complete seizure control without side effects which may be either idiosyncratic, or due to intoxication, or chronic. Serum anticonvulsant levels are a useful guide to therapy – phenytoin (40–80), carbamazepine (20–50), phenobarbitone (40–170), ethosuximide (200–600). Valproate 300–600, oxcarbazepine 50–125, lamotrigine 4–60 mmol/litre. If the optimum level of a single, first line drug does not control seizures, or if side-effects develop, the initial drug should be substituted with another first line anticonvulsant. If the second drug also fails to control seizures monotherapy with a third anticonvulsant, or combination therapy with two first line drugs should be tried.

If a combination of two first-line drugs is unsuccessful, one of the second-line drugs may be considered.

Table 35: Anti-epileptic drugs

Drug	*Indications*	*Dosage*	*Side-effects/comments*
Carbamazepine	Localization-related	200 mg/d increased by 200 mg at 2wks intervals	Ataxia, rash, conduction defects, neutropenia, SIAHS
Oxcarbamazepine	Localization-related	300 mg/d increased by q3d (max 1200/d)	Side effects less common
Sodium valproate	Localization-related Idiopathic generalized	200 mg bd increased by 200 mg q2 wks	Tremor, obesity, hair loss, menstrual changes, thrombocytopenia
Divalproex sodium	Progressive myoclonic		
Phenytoin	Localization-related	200 mg/d increments of 25–50 mg as per therapeutic monitoring 750–1000 mg o.d.	Gum hypertrophy, acne, hirsutism, facial coarsening, ataxia
Lamotrigine	Localization – related Idiopathic generalized	25 mg/d, in pts on valproate 10 mg/day increases by 25 mg/d q2 wks	Rash, multisystem allergic disorder
Ethosuximide	Absences only	250 mg/d increased by 25 mg q2 wks	GI upset, ataxia Cognitive slowing, mood and behaviour changes, habituation
Barbiturates	Status only		
Clobazam	Localization-related Idiopathic generalized	10-20 mg bd for 1–3 days short-term	Sedation, disinhibition (in children and those with learning disability). It may prevent postictal psychosis.
Clonazepam	Myoclonus only	0.5 mg maximum initially nocte	– – –
Gabapentin	Localization-related	300-400 mg/d increased 400 q/wks Max. 1200 mg tds.	Ataxia, nightmares Wt. loss, slowing, speech difficulties, paraesthesia. Useful in those at risk to interactions
Topiramate	Localization-related Idiopathic generalized	25 mg/d increased by 25 mg q2 wk to 100 mg bd.	Anxiety, tremor, speech difficulties
Tiagabine	Localization-related	35–40 mg/d in divided doses increase 5 mg q1 wk,	Mood changes, psychosis, visual field defects
Levetiracetam	Localization-related Generalized myoclonic seizures	250 mg/d increased to 2–3 g/d	Irritability, somnolence, dizziness
Zonisamide	Localization-related Myoclonic seizures	50 mg/d increased to 300–400 mg/d in bd doses	Dizziness. Renal calculi
Lacosamide	Adjuvant in uncontrolled partial seizures	400–600 mg/d	GI irritation, prolonged interval
Rufinamide	Lennox-Gastaut syndrome	3200 mg/day	Leukopenia, QT shortening

Note: Any drug may cause headaches, diplopia, unsteadiness, nausea, lethargy, sedation, dizziness and unpredictable responses. Vigabatrin therapy may be associated with loss of peripheral visual fields as a result of retinal toxicity and is not recommended.

Drug withdrawal – should take place slowly over 2 to 3 months. If patient is receiving more than one drug, each one should be withdrawn individually.

Pregnancy – No antiepileptic drug can be considered safe in pregnancy; valproate may be more teratogenic than others. The risk may be higher in women who have previous history of foetal malformations. Doses should be kept at the minimum required in the first trimester. Measurement of drug levels helps guide dose increases to achieve a level that previously controlled seizures, if these recur. Postnatally, doses must be reduced again over weeks to prevent toxicity. Supplemental folate 5 mg/day may reduce risk of malformation.

All women treated with enzyme-inducing drugs (and possibly all other antiepileptic drugs) should be given vitamin K1, during last month of pregnancy, and the newborn 1 mg i.m. to prevent vit. K deficiency bleeding.

Breast-feeding – Lamotrigine, benzodiazepines and barbiturates reach significant levels in breast milk.

Elderly – Incidence of onset of epilepsy shows a second peak in the elderly. Only lower doses of drugs can be tolerated, and interactions with concomitant medications

are common. Carbamazepine and valproate are preferred drugs.

Electrocorticography surgery – Electrodes are placed in affected area of the brain to study how it functions or malfunctions. Using this imaging, surgeons get a precise mapping of the affected part of the brain and operate accordingly.

Social and psychological management – Attention to doubts and fears of the patient. No imposition of unnecessary restrictions. Education of the patient and his relatives about the nature of the illness, its precipitating factors and its consequences.

Surgical Treatment

It is considered in patients refractory to medical treatment. It includes temporal lobectomy in mesial temporal lobe sclerosis. For focal seizures arising from extratemporl region lesionectomy done. In these cases localization of focus is important, done with help of video-EEG, high resolution MRI study, SPECT, PET study.

Deep brain stimulation, Vagal nerve stimulation and laser thermoablation are newer alternatives to surgical treatment in refractory cases.

Status epilepticus – is the repeated occurrence of seizures without recovery in between. Status may be generalized convulsive tonic-clonic, partial motor (epilepsia partialis continua), non-convulsive or absence. Except for absence status, these conditions are medical emergencies.

Clinical features: SE can be divided into four stages depending on the duration for which seizures continue.

1. *Prodromal phase* – In patients with established epilepsy, tonic-clonic SE seldom develops without warning. There is usually a prodromal stage in which seizures become more frequent.
2. *Early status* – Once SE has developed the first 30 minutes comprise of the early stage.
3. *Established status* – is status which has continued for 30 minutes in spite of early stage treatment.
4. *Refractory status* – The stage is reached, if seizures continue for 60–90 minutes after initiation of therapy.

Management

General Measures

- Avoid hypoxia: Protect patient from injury. Semiprone, head down position. Maintain airway. Administer O_2.
- Monitor ECG, blood pressure, oximetry and temperature.
- Establish intravenous access in large veins. Take blood for electrolytes, glucose, calcium, magnesium, full blood count, anti-epileptic drug levels, alcohol and toxicology screen, and cultures as appropriate. Urea and electrolytes, blood glucose, calcium and phenytoin levels are obtained urgently.
- Check glucose and immediately correct any hypoglycaemia with 50% glucose, up to 50 mL i.v. over, 1–2 minutes into a large vein.
- If poor nutrition or alcohol abuse is suspected, administer thiamine 250 mg (10 mL) i.v. over 10 minutes.
- Check blood gases.

Important

- Investigate the cause of status.
- Reinstate any recently withdrawn anti-epileptic drug.
- Continue existing anti-epileptic drugs.
- Start maintenance therapy promptly.

Note

- 25% of patients with so-called refractory status epilepticus referred to specialist units have pseudostatus epilepticus.
- EEG is useful in the diagnosis of status and pseudostatus.
- The iatrogenic complications of inappropriate treatment are significant.

Specific Drug Therapy

- Lorazepam 4 mg IV over 2-3 minutes or IV Diazepam 5 mg IV. Repeat dose, if necessary. If IV access not possible give Midazolam 10 mg intranasally or IM.
- Give IV phenytoin 15–20 mg/kg or IV Fosphenytoin 20 mg/kg in infusion at rate of less than 50 mg/min (phenytoin).
- Alternatives to IV phenytoin are Valproate 500-1000 mg IV bolus or Levetiracetam 1gm bolus.

Refractory status - If seizures continue (more than 20 minutes), then intubate and give one of the following:

(a) Midazolam drip IV. Load with 0.2 mg/kg and infuse at rate of 0.03-0.2 mg/kg/hr or

(b) Propofol IV. Load 1–2 mg/kg repeat every 5 mts till seizures stop, followed by IV infusion 2-10 mg/hr. Propofol is a short acting anaesthetic agent with a rapid metabolic clearance and less pronounced hypotensive effect compared to thiopentone or

(c) Phenobarbitone IV bolus 6–8 mg/kg at a rate not more than 60 mg/min.

Partial (local) minor SE consists of frequent seizures involving an extremity or facial muscles with preservation of consciousness and no tendency for generalisation. *Tr.*

– Phenytoin po during an 8–12 hour period followed by maintenance dose of 300–400 mg/day.

Non-convulsive SE is essentially a behavioural manifestation without significant motor involvement.

12. CEREBROVASCULAR DISEASES

The term cerebrovascular disease embraces:

1. Disease of the cerebral arteries (atheroma being the commonest cause) and of the major neck vessels supplying the brain.
2. Diseases of the heart which may adversely affect blood supply to the brain by changes in blood pressure or as a source of emboli.
3. Disorders of the blood which may lead to impaired clotting, causing hemorrhage, hyperviscosity or hypercoaguable states, which increase tendency for cerebral thrombosis.

Stroke is defined as an acute focal neurological deficit resulting from cerebrovascular disease and lasting more than 24 hours (or causing earlier death). Stroke is not a diagnosis, but a clinical syndrome with numerous causes: Mainly:

- Cerebral infarction
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Cerebral venous thrombosis

Table 36 lists the main risk factors for stroke.

ISCHEMIC STROKE

Transient Ischemic Attacks (TIAs)

Refer to an episode of acute neurological deficit. MRI must not show evidence of acute ischemia irrespective of the time period of recovery, occurring as a result of reduced flow to a vessel from fall in perfusion pressure (e.g. cardiac arrhythmia associated with localized stenotic cerebrovascular disease), or blockage of passage of flow by embolism arising from plaques in aortic arch, or extracranial vessels or from heart. If flow is restored within the critical period, ischemic symptoms reverse themselves, otherwise infarction may occur. Since there is no serious persisting disability, the term reversible ischemic neurological deficit (RIND) is used in such cases.

Cardiac embolism from thrombus in left atrium or ventricle.

Table 36: Risk factors for stroke

Major risk factors
• Hypertension
• Cardiac disease – Ischemic heart disease, atrial fibrillation
• Transient ischemic attacks
• Cigarette smoking
• Alcohol
• Hyperlipidemia – elevated LDL cholesterol
• Oral contraceptives
• Obesity
• Sedentary life
• Diabetes mellitus
Associated risk factors
• Diabetes mellitus
• Previous stroke
• Raised haematocrit
• High plasma fibrinogen
• Antiphospholipid antibodies (APLA)
• Asymptomatic carotid arterial lesions (carotid bruits)

Large Artery Disease

Atherosclerosis of the major vessels supplying the brain is the other main source of cerebral embolism. The emboli are usually platelet aggregates or thrombus formed on atherosclerotic plaques, but occasionally comprise cholesterol and other atherosclerotic debris.

Dissection of vertebral or carotid artery can occur spontaneously or following neck trauma. Fibromuscular dysplasia may predispose to dissection.

Major vessel occlusion may be asymptomatic or may cause embolic TIA, or minor or major stroke. It can also result in a stepwise progression of symptoms from propagation of thrombus, for example, vertebral artery occlusion may initially cause only a TIA, but if the thrombus spreads to the basilar artery the patient may develop a major brainstem stroke a few hours or days later.

Middle cerebral artery occlusion is usually the result of cerebral embolism, but can result from localized intracranial atherosclerosis (Fig. 13).

Small Vessel Disease (Lacunar Infarcts)

Occlusion of small penetrating arterioles, usually secondary to hypertension or diabetes mellitus, (microatheroma and hypohyalinosis) leads to small infarcts in subcortical white matter, internal capsule, basal ganglia and pons, termed 'lacunar infarcts' (infarcts < 1 cm in diameter)

Cl. Fs. All on ipsilateral side – (a) Motor stroke symptoms develop in step-wise fashion (stuttering). Hemiparesis or hemiplegia at times only arm and leg weakness without face. Motor aphasia, if lesion in genu and anterior limb of internal capsule. (b) Ataxic hemiparesis – (cerebellar symptoms with weakness more of leg than arm). (c) Sensory stroke due to thalamic lesion and posterior internal capsule lesion – numbness and tingling on one side of body, less often pain or burning sensation. (d) Mixed stroke – Hemiparesis or hemiplegia with diminished sensations. Dysarthria and a clumsy hand or arm due to infarction in the ventral pons or in the genu of the internal capsule

Figure 14 and Table 37 give arterial territories and neurological deficits.

Figure 14 shows the origin of the great vessels from the aortic arch, the circle of Willis and its branches, the areas of the brain supplied by the major intracerebral arteries.

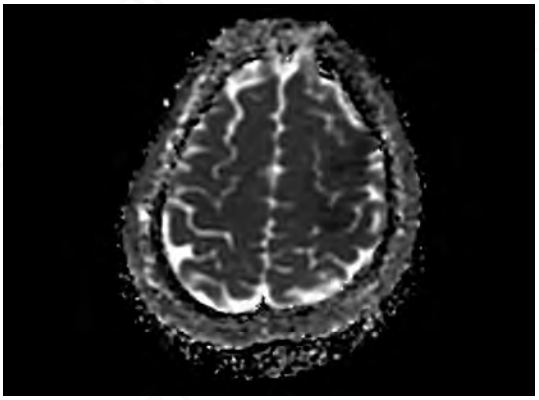


Fig. 13: MRI ADC image showing hypointensity in left MCA territory suggestive of acute infarct

The distribution of anterior (A), middle (M) and posterior (P) cerebral areas are shown.

Table 38 gives pathophysiology of strokes.

Less common Causes of Stroke

Haematological abnormalities – that promote thrombosis, e.g. polycythemia and thrombocythemia. Anticardiolipin antibodies may cause acquired abnormalities of thrombolysis and are associated with stroke in younger patients. Thrombophilia may cause cerebral venous thrombosis. Low dose oestrogen-containing oral contraceptives do not increase risk of stroke significantly in healthy women, but may do so in those with other vascular risk factors. Sickle cell anemia is common cause of stroke in children.

Subclavian steal – is an uncommon cause of hemodynamic symptoms. If the subclavian artery is occluded or stenosed before the origin of the vertebral artery, arm exercise may cause retrograde flow down the vertebral artery at the expense of the vertebrobasilar circulation, resulting in brainstem TIA.

Migraine – is a rare cause of cerebral infarction. Headache is common in ischemic stroke and may be caused by collateral vasodilatation or carotid dissection.

Vasculitis – is a rare cause of both haemorrhagic and ischemic stroke. Systemic features of the underlying vasculitis usually suggest the diagnosis in SLE, polyarteritis nodosa and giant cell arteritis, but absent in isolated or granulomatous angiitis of the CNS. Cardiac embolism from endocarditis and acquired thrombophilia with anticardiolipin antibodies are other possible causes of stroke in SLE.

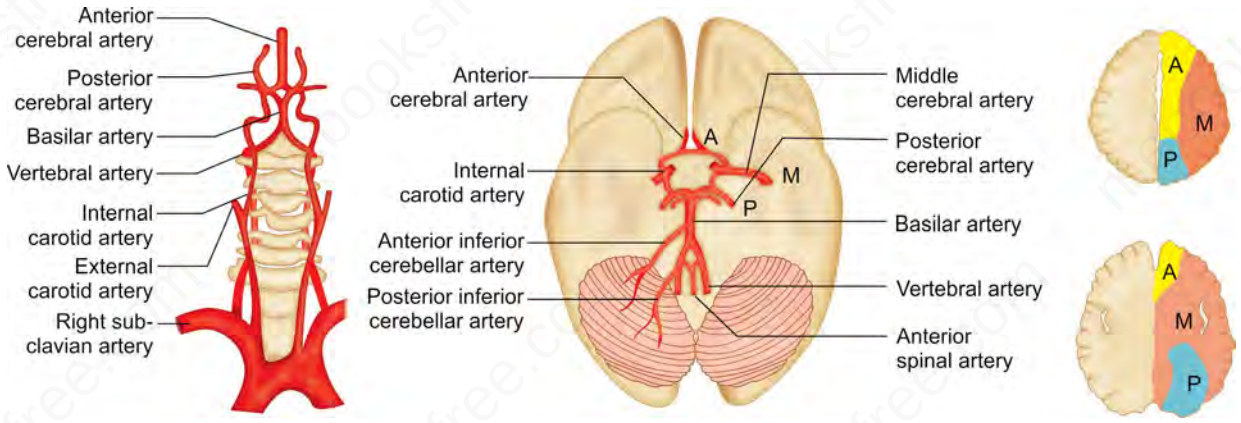


Fig. 14: Cerebral circulation

Table 37: Arterial territories and neurological deficits

Arterial territory and area supplied	*Syndrome if total territory involvement*
Internal carotid	
Ophthalmic artery: Retina	Amaurosis fugax, altitudinal field defects in one eye, uniocular blindness
Middle cerebral artery: (Fig. 15) Parietal lobe, frontal lobe, sup. Temporal lobe	Contralateral UMN facial weakness, hemiplegia (arm>leg), hemianopia, aphasia (dominant hemisphere) or visuospatial disorientation (non-dominant hemisphere)
Anterior cerebral artery: Anterior and superior medial frontal lobe	Contralateral foot and leg weakness or hemiplegia (leg>arm), grasp reflexes, incontinence, abulia, apathy, akinetic mutism
Vertebrobasilar territory	
Posterior cerebral artery: (Figs. 16 and 17) Occipital lobe, inferior temporal lobe part of thalamus	Contralateral hemianopia Cortical blindness, if bilateral Amnesia (especially, if bilateral ischemia). Contralateral sensory loss. Thalamic pain, thalamic aphasia.
Posterior inferior cerebellar artery: Lateral medulla, inferior cerebellum	Vertigo and vomiting, dysphagia. Ipsilateral palatal weakness Ipsilateral facial sensory loss (variable) with contralateral hemisensory loss below neck Ipsilateral Horner's syndrome Ipsilateral cerebellar signs
Vertebral and basilar artery: Brainstem and cerebellum	Diplopia, ophthalmoplegia or gaze palsies Nystagmus, vertigo, vomiting Dysarthria, dysphagia, bulbar cranial nerve weakness Ipsilateral facial numbness and weakness (LMN) Hiccups and resp. failure Coma Contralateral hemiparesis or tetraparesis Contralateral or bilateral sensory loss. Normal consciousness, cognitive function and visual fields.
Small vessel (lacunar) syndromes (small stroke)	
Pure motor stroke: Internal capsule or pons	Hemiparesis (face and arm with/without leg) Dysarthria and dysphagia.
Pure sensory stroke: Thalamus, internal capsule	Hemisensory impairment Thalamic pain.
Sensorimotor stroke: Basal ganglia and internal capsule	Combination of above
Ataxic hemiparesis: Internal capsule or pons	Hemiparesis, ipsilateral limb ataxia, dysarthria, clumsy hand, gait ataxia.
Movement disorders: Basal ganglia	Hemichorea, hemiballismus, gait ataxia.

Watershed infarction – During transient circulatory arrest or profound anoxia, infarction can occur at border zone of arterial territories, particularly in parietooccipital region which is the watershed between middle, anterior and posterior cerebral arteries. Usual picture is of visual disorientation or cortical blindness, often associated with visual field defect and sensory impairment.

Multi-infarct dementia – A succession of minor vascular events can lead to dementia. Vascular dementia may also result from diffuse small vessel disease which leads to ischemia of deep white matter and basal ganglia (Binswanger's disease or 'subcortical arteriosclerotic encephalopathy'). There may not be a clear history of stroke, but dementia is usually marked by step-wise deterioration with periods of improvement. CT or MRI shows patchy or diffuse abnormalities in the periventricular regions (leukoaraiosis).

Silent cerebral infarction – Many middle-aged and elderly patients with hypertension without a history of stroke or TIA have small lacunar infarcts or patchy ischemic periventricular imaging abnormalities (leukoaraiosis) on CT or MRI.

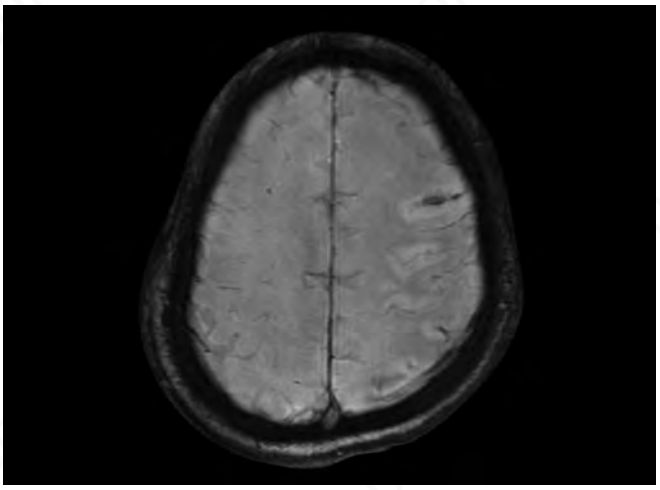


Fig. 15: MRI SWI image showing acute infarct with haemorrhagic transformation in MCA territory

COMPLICATIONS OF STROKE

Cerebral oedema – should be suspected, if a patient with a large infarct or haemorrhage experiences a lucid interval of 24–48 hours and then shows a decline in consciousness. Swelling of infarcted tissue compresses surrounding tissues and blood vessels, and may compress the brainstem leading to coma and death.

Haemorrhagic transformation – of an infarct may occur as a result of spontaneous or therapeutic thrombolysis, but does not necessarily result in clinical deterioration (Figs. 18 and 19).

Pneumonia – may occur due to aspiration from swallowing difficulties.

Oedema of – weak limbs is common, and has a partially autonomic basis.

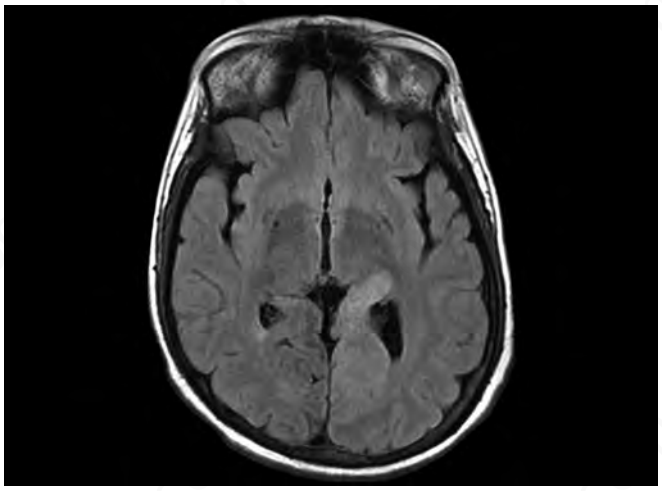


Fig. 16: PCA territory infarct MRI axial view T2 image

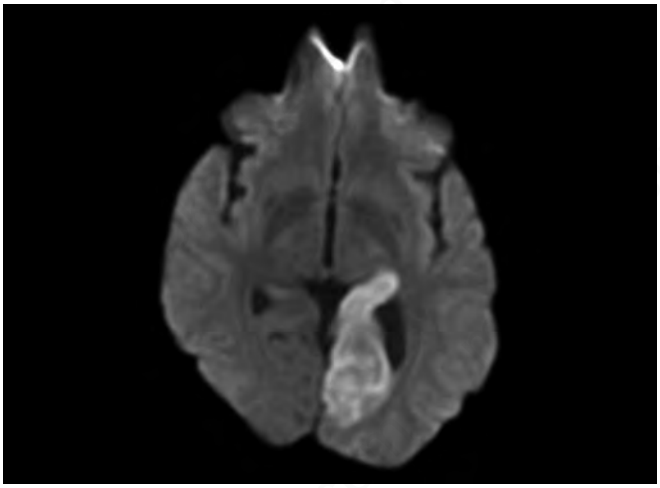


Fig. 17: PCA territory infarct MRI DW image

Table 38: Pathophysiology of stroke

Causes	*Common*	*Less common*
Cerebral embolism		
Carotid, vertebral or basilar arteries	Atherosclerotic stenosis and ulceration, atherothromboembolism	Dissection Fibromuscular dysplasia Trauma
Left ventricle	Myocardial infarction	Cardiomyopathy
Aortic or mitral valves	Rheumatic heart disease Mitral valve prolapse Infective endocarditis	Prosthetic valves
Left atrium	Atrial fibrillation	Sino-atrial disease Myxoma Aneurysm

Contd...

Contd...

Causes	*Common*	*Less common*
Deep vein thrombosis (paradoxical embolism)		Cong. septal defects Patent foramen ovale
Trauma		Fat or air emboli
Iatrogenic		Cardiac surgery Cardiac catheterization Cerebral angiography
Vasospasm	Subarachnoid hemorrhage	Migraine
Vasculitis		Giant cell arteritis SLE, PAN Other causes of vasculitis Radiation, granulomatous angiitis, TAO, Moyamoya disease Takayasu's disease
Hemodynamic	Carotid occlusion	Severe hypotension Cardiac arrest
Cerebral venous thrombosis	Dehydration Intracranial sepsis	Hypercoagulable states Invasion by tumours
Local arterial thrombosis		
Major arteries	Atherosclerosis	Dissection, fibromuscular dysplasia
Small vessels	Hypertension Arteriosclerosis Diabetes mellitus	
Hypercoaguable states causing arterial and venous stroke	Congestive heart failure Malignancy Polycythemia Thrombocythemia Smoking	Pregnancy Oral contraceptives Protein C deficiency Protein S deficiency Antithrombin III deficiency Sickle cell disease Homocystinuria
Intracranial hemorrhage		
Subarachnoid haemorrhage	Saccular aneurysm A-V malformation Trauma	Haematological abnormalities 'Border zone' infarction Subclavian steal Migraine Vasculitis
Intracerebral haemorrhage	Hypertension Aneurysm A-V malformation Anticoagulant therapy Thrombolytic therapy	Bleeding disorders Vascular tumors Vasculitis Amyloid angiopathy Moyamoya disease

Shoulder pain – may develop as a result of poor posture and spasticity.

Cognitive Effects of Stroke

- *Dysphasia, dysgraphia, dyslexia and dyscalculia* lead to communication difficulties in dominant left hemisphere lesions.
- *Neglect* leads to patients ignoring the environment and their limbs on the hemiparetic side, particularly in non-dominant right hemisphere lesions.
- *Aprosody* (failure to understand or express meaning conveyed by variations in tone, rhythm and accent of speech) may result from non-dominant right hemisphere lesions.
- *Spatial disorientation* may lead to the patient becoming lost, particularly in unfamiliar surroundings.
- *Memory impairment* leads to confusion and disorientation.
- *Anxiety and depression* are common reactions to stroke, but depression may also have an organic basis related to frontal or limbic system.
- *Emotional lability* is common and often leads to tears (or occasionally laughter) precipitated by minor emotional stimuli.

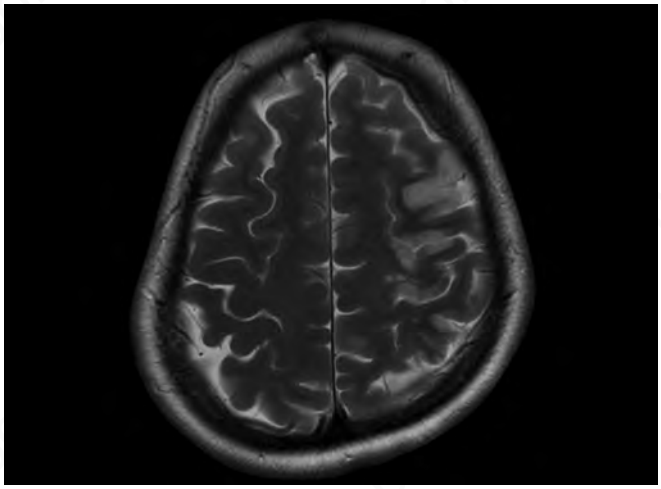


Fig. 18: Acute infarct MCA territory MRI axial view T2 image

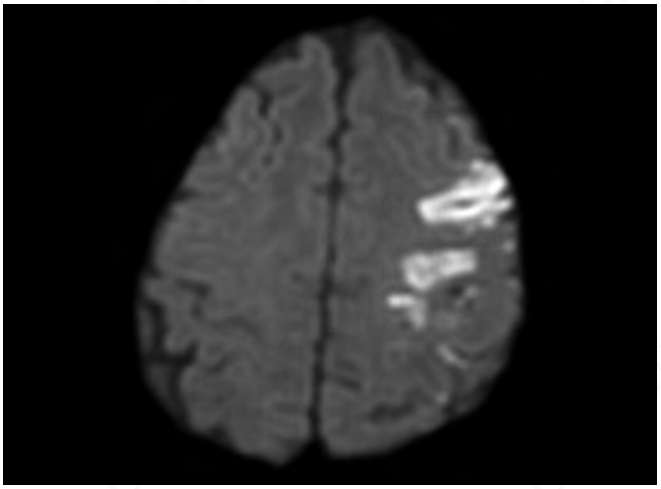


Fig. 19: Acute infarct MCA territory MRI DW image

Differential Diagnosis

TIA

Focal epilepsy – causes transient symptoms, which are usually positive (tingling or jerking) in contrast to the negative symptoms in TIA (numbness or paralysis).

Migraine – Isolated focal visual or sensory migraine aura without headache may mimic TIA, but the focal symptoms of migraine progress over 10–30 minutes.

Meniere's disease and benign positional vertigo – TIA should only be diagnosed, if the vertigo is accompanied by other brainstem symptoms (e.g. diplopia, dysarthria), dysphagia, limb weakness.

Hypoglycemia – may cause hemiparesis for about one hour after hypoglycemia has resolved.

Multiple sclerosis – may cause paroxysmal visual blurring or limb symptoms.

Stroke

Space-occupying lesion – About 5% of patients presenting with stroke-like symptoms have a subdural hematoma, tumour or cerebral abscess, granuloma (neurocysticercosis, tuberculoma). The diagnosis is made only on CT or MRI.

Multiple sclerosis – may present with hemiplegia, sensory impairment or brainstem symptoms that mimic stroke. Usually symptoms occur over a few days. Abnormal visual evoked potentials, characteristic MRI appearance and oligoclonal immunoglobulins in CSF may elucidate the diagnosis.

Hysteria – seldom presents with stroke-like symptoms but should be considered, if there are marked fluctuations and signs inconsistent with organic disease.

Table 39: Causes of hemiplegia

A. Sudden onset:
1. Vascular causes.
2. Intracranial infection – encephalitis, meningitis.
3. Trauma – depressed fracture.
4. Hypertensive encephalopathy.
5. Post-epileptic paralysis (Tod's palsy).
6. Multiple sclerosis.
7. Uraemia.
8. Hysterical.
B. Slow onset:
1. Cerebral tumour.
2. Cerebral abscess.
3. Internal carotid artery occlusion sometimes.
4. Chronic subdural haematoma.
5. Meningitis, encephalitis.
6. Chorea.
7. General paralysis of insane.
8. Congenital defects – diffuse sclerosis, cerebral agenesis.

HEMIPLEGIA

Causes of hemiplegia are listed in Table 39.

Determination of the Side of Hemiplegia in an Unconscious Patient

Away from the paralysed side – Conjugate deviation of eyes.

On the hemiplegic side – (1) Cheek puffs out during respiration. (2) Nasolabial fold obliterated. (3) Corneal reflex diminished. (4) Pain stimulation less effective. (5) More

absolute flaccidity of limbs (dropping tests). (6) Paralysed leg extended and assumes position of external rotation while healthy one tends to be semiflexed. (7) Pupil large on side of haemorrhage. (8) Eyelid release test – Eyelid slides down slowly after both the eyelids are pulled up and released simultaneously. (9) Temperature of paralysed side usually higher.

Investigation and Diagnosis of a Case of Cerebrovascular Accident

I. History

1. *Age* – In a young patient consider:
   - Cardiac disease – Infective endocarditis, atrial fibrillation, mitral valve stenosis or prolapse.
   - Vascular disease – Severe hypertension, hypercoagulable state, vasculitis, e.g. SLE, arteritis of intracranial vessels – T.B., syphilis, pyogenic.
   - A-V malformation/Aneurysm.
   - Intracranial space occupying lesion
   - Encephalitis, e.g. HSV type 1.
   - Post-ictal.
   - Migraine (classical).
   - Hysteria.
   - Hyperventilation (may simulate TIA).
2. *History of previous minor episodes* – may suggest disease of caroticovertebral system, of embolic disease from these arteries or from the heart, of progressive cerebral arteriosclerosis or effects of hypertension. History of migraine or epilepsy in young patient may suggest intracranial A-V malformation. History of ischemic heart disease, intermittent claudication, bleeding tendency, diabetes or of symptoms suggesting intracranial tumour should be elicited.
3. *History of head injury* – Depressed fracture and subdural haematoma.
4. *History of drugs* – e.g. contraceptive pills, hypotensive drugs, anticoagulants.
5. *Family history* – History of strokes and an early age of onset may suggest familial trait to early atherosclerosis.
6. *Past history* – of diabetes, hypertension or cardiac disease, or of anaemia or fluid loss which may serve as precipitating factors.
7. *Symptoms* –
   (a) *Mode of onset* – Catastrophic in haemorrhage, progressive in thrombosis, instantaneous in embolism (maximum at onset).

Table 40: Causes of transient hemiplegia

• Transient cerebral ischaemia (TIA)
• Embolism from the heart
• Migraine
• Epilepsy
• Structural intracranial disorders such as tumour, chronic subdural haematoma, giant aneurysm or angioma
• Polycythemia, thrombocythemia or sickle cell disease
• Anaemia
• Hyperviscosity syndromes
• Hypoglycemia
• Hypertensive encephalopathy
• Hysterical hyperventilation
• Multiple sclerosis
• Congestive attacks of GPI.

   (b) *Transient hemiplegia* – or transient focal neurological disturbance may be due to coditions listed in Table 40.
   (c) *Headache* – In cerebral haemorrhage the headache is intense with accompanying stiffness of neck, in carotid insufficiency the headache is temporal and usually on the side of the ischaemia, in basilar artery insufficiency the headache is occipital or suboccipital. Severe headache is felt in subarachnoid haemorrhage at the onset. Headache and vomiting may occur in cerebral tumour or abscess and subdural haematoma. Vomiting preceding a stroke favours a diagnosis of haemorrhage.
   (d) *Chest pain* – suggests associated myocardial infarction.
   (e) *Symptoms suggestive of hysterical hemiplegia* – (i) Onset after emotional shock. (ii) Hysterical type of rigidity. (iii) Plantars never extensor. (iv) Hoover's contralateral leg sign – when patient attempts to raise the paralysed leg, the opposite heel does not make counter pressure backwards on the palm of the examiner's hand as in organic hemiplegia. (v) Contraction of platysma present on affected side. (vi) Hysterical gait.
   (f) *Coma* – Sudden or rapid loss of consciousness at onset common in subarachnoid hemorrhage, intra- cerebral hemorrhage and brainstem strokes. In subdural hematoma increasing drowsiness and spontaneous variations in coma, the patient may pass from consciousness into coma and back again in a few hours.

(g) *Seizures* – in tumour.

(h) *Fever* – in meningitis, encephalitis and cerebral abscess.

(i) *Involuntary movements* – in encephalitis and chorea. In chorea usually upper limb alone is paretic.

(j) *Mental symptoms* – encephalitis and sometimes tumour.

(k) *Abdominal pain and melena* – suggest gastrointestinal bleeding as the precipitating cause.

II. Physical examination

A. Neurologic

1. *State of consciousness* – may vary from full alertness to lethargy, stupor, semiconsciousness or coma.
2. *Speech* – should be evaluated to differentiate between slurred dysarthric speech and dysphasic speech. The former is more likely to be found in diseases of brainstem, the latter in involvement of dominant cerebral hemisphere.
3. *Neck rigidity* – subarachnoid hemorrhage, and meningitis.
4. *Eyes* – (a) *Movements* – Most spontaneous nystagmus and unusual eye movements are due to brainstem disease, but eye deviation away from the side of hemiparesis is common with recent infarction in middle cerebral artery territory. Eyes deviated to side of hemiplegia suggests pontine lesion. (b) *Pupils* – Ipsilateral Horner's syndrome may be found in acute carotid thrombosis but may also indicate brainstem disease. Pupillary enlargement occurs early in paralysis of 3rd cranial nerve associated with aneurysm or temporal lobe herniation. (c) *Fundi* – for early papilloedema, optic atrophy, emboli in retinal arteries, subhyaloid hemorrhage.
5. *Focal neurological deficit* – Test for hemiparesis, hemianopia or hemisensory loss.

B. General

1. *Blood pressure* – for arterial hypertension. BP should be checked in both arms because of possibility of aortic arch syndrome or subclavian steal syndrome.
2. *Heart* – for cardiac arrhythmia such as atrial fibrillation, or recent myocardial infarction, atrial myxoma or valvular disease.
3. *Arterial pulses* – (a) For peripheral vascular disease. (b) In neck – for carotid artery stenosis. (c) Temporal arteries – Absent pulsation in external carotid occlusion. Tortuous in atheroma. Tender, thickened, poorly pulsatile in cranial arteritis. Tortuous, dilated highly pulsatile temporal artery when the artery is feeding an arteriovenous malformation, or a meningioma.
4. *Bruits* – due to stenosis. Over carotid and subclavian arteries, bruit produced by stenosis in vertebral arteries. Auscultation of orbit or skull if intracranial arteriovenous malformation or arteriovenous shunt.
5. *Signs of head injury.*
6. *Ophthalmodynamometry* –for recording ophthalmic artery pressure. A difference in the pressure of the two ophthalmic arteries would suggest a disease in the internal carotid artery on the side of the low pressure.

III. Investigations

CT scan – to establish the pathological diagnosis (infarction or hemorrhage) (Figs. 20 and 21) and to exclude other conditions that may mimic stroke (e.g. subdural hematoma, intracranial tumour). All patients must undergo scanning within 24 hours. The site of infarction can be identified and may give clues to the pathogenesis (e.g. border zone infarct suggests a hemodynamic origin, multiple cortical infarcts a cardiac source of emboli). In suspected SAH, scanning may show subarachnoid blood, and the need for LP may hence be avoided.

With CT, hemorrhage can be seen within a few minutes as an area of increased attenuation, but after a few weeks the lesion becomes of low attenuation, and it may be impossible to distinguish infarct from hemorrhage, if CT is not performed within 2 weeks.

An urgent CT scan is required to exclude surgically treatable conditions (e.g. SAH, cerebellar haematoma, space-occupying lesion). *Indications* – (i) Progressive or fluctuating symptoms. (ii) Drowsiness or coma. (iii) Brainstem symptoms or signs. (iv) Papilloedema, neck stiffness or fever. (v) Severe headache. (vi) Unexpected deterioration.

Magnetic resonance techniques – MRI is more sensitive to small areas of ischemia than CT and can detect traces of old hemorrhage (hemosiderin deposits) indefinitely. New MRI sequences are sensitive to changes of cerebral ischemia and can provide information about the underlying pathophysiology.

- Diffusion weighted imaging uses a sequence of magnetic resonance pulses that are sensitive to intracellular oedema (Figs. 22 and 23). It shows areas of critically ischemic brain tissue as intensely bright increases in signal within minutes of onset ('light-bulb' sign). In acute stroke it is the investigation of choice.

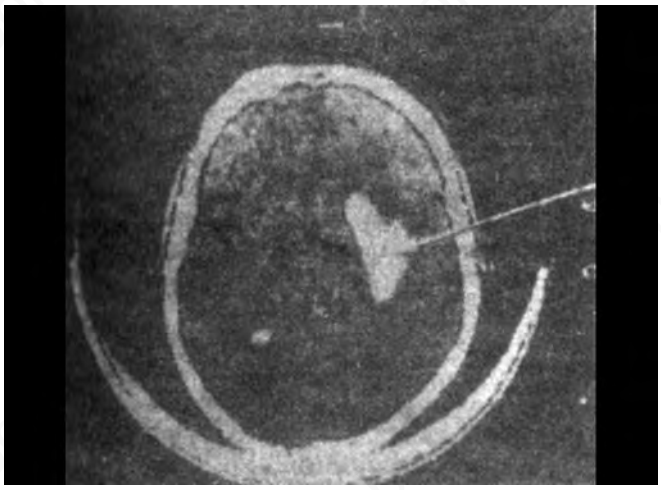


Fig. 20: CT scan showing a cerebral hemorrhage (white area) in left basal ganglia region

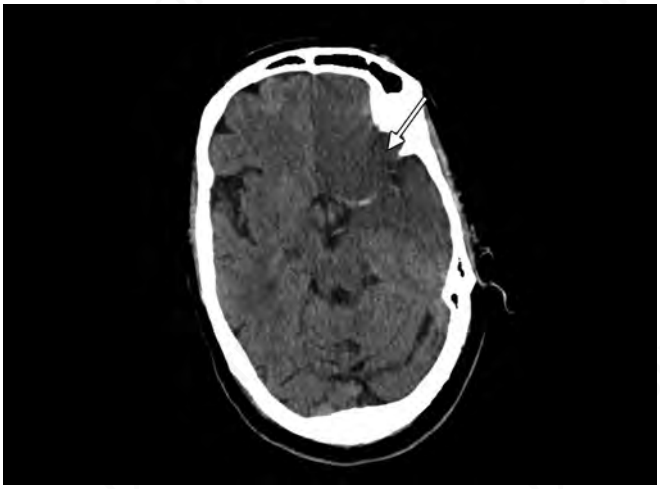


Fig. 21: Axial CT image showing hyperdence left MCA in a case of acute infarct

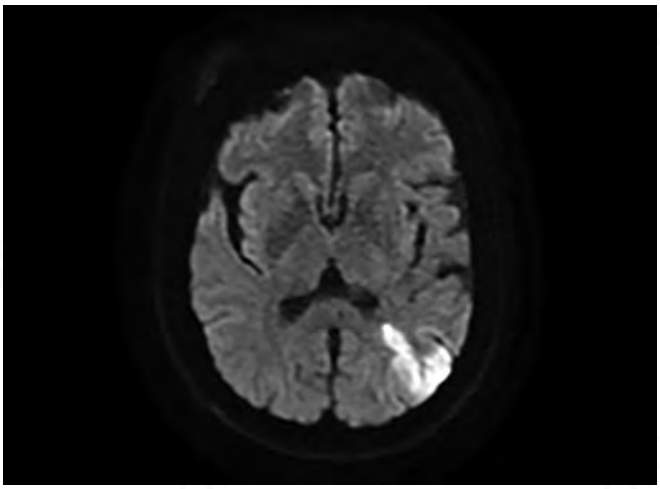


Fig. 22: Acute infarct in left PCA territory showing diffusion restriction on MRI DWI

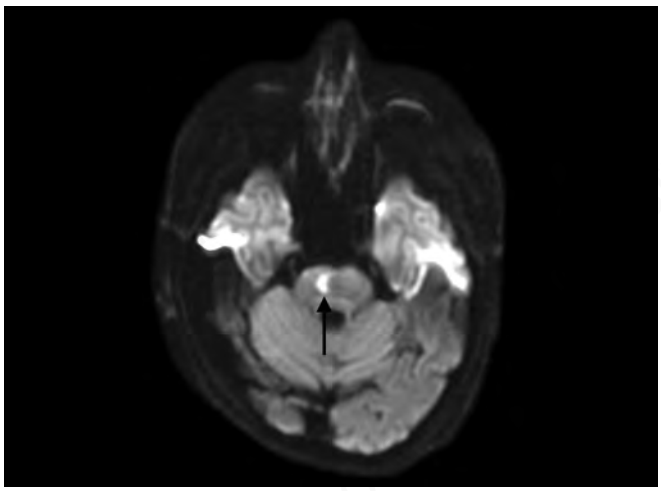


Fig. 23: Acute infarct in pons DW MRI image

- Perfusion MRI shows low cerebral blood flow by measuring the distribution and transit time of i.v. contrast.
- MR spectroscopy measures the concentration of certain chemical entities within the brain, for example it is sensitive to the presence of lactate (a marker of ischemia not found in normal brain), and can measure the concentration of N-acetyl aspartate (a marker of intact functioning neurons).
- Intracranial magnetic resonance angiography (MRA) can be used to confirm or exclude intracranial vessel occlusion.
- Combination of diffusion-weighted MRI, perfusion MRI and MRA (multimodal imaging) can be performed within 20 minutes. These techniques would allow targeting for treatment those most likely to benefit, e.g. thrombolysis might be appropriate only in patients with both vessel occlusion on MRA and perfusion- diffusion mismatch.

Carotid ultrasonography – using duplex imaging and Doppler measurement of blood flow in patients with TIA and stroke in the carotid territories, to identify carotid artery stenosis, occlusion and dissection.

MRA – provides an alternative to ultrasound for non-invasive detection of carotid artery stenosis and occlusion or dissection. It can also be used to image distal vertebral and intracranial vessels.

Digital subtraction angiography – (a) If there is doubt after non-invasive imaging (Fig. 24). (b) To confirm occlusion or dissection. (c) In subarachnoid and intrac-

ranial hemorrhage to diagnose the source of bleeding, to detect aneurysms. (d) In suspected vasculitis occasionally. (e) In younger patients with recurrent or unexplained symptoms.

Measurement of O_2 saturation by pulse oximetry

Blood tests

- FBC, including platelet count to detect polycythemia, platelet disorders and infection.
- ESR – if raised suggests infection, systemic vasculitis or carcinoma and should lead to further investigations (e.g. autoantibody screen, CXR).
- Blood sugar, electrolytes and kidney function.
- Fasting lipids.
- Clotting screen – in intracerebral hemorrhage and SAH.

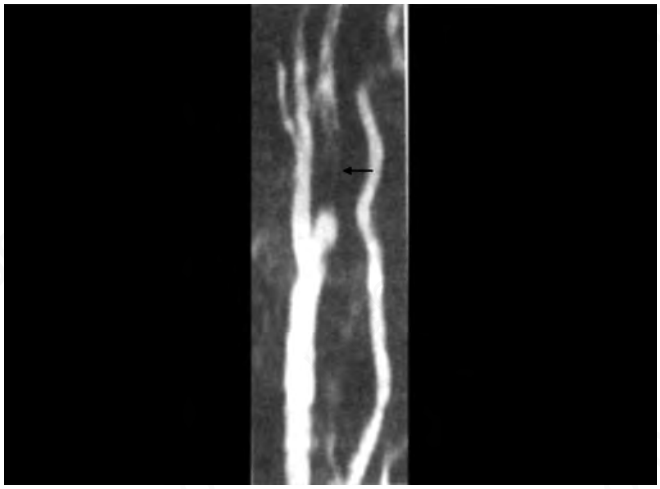


Fig. 24: Magnetic resonance angiogram showing severe left internal carotid artery stenosis in the neck

- Thrombophilia screen – for anti-cardiolipin antibodies, protein C and protein S and antithrombin III levels and factor V Leiden polymorphism, is indicated in patients under age of 30 years or in older patients with TIA or ischemic stroke.
- Syphilitic serology.
- Blood cultures – if infective endocarditis is suspected.

Cardiac investigation – to detect sources of cardiac embolism. (a) ECG – to detect atrial fibrillation. (b) Echo – in patients under age of 60 or older patients with significant cardiac abnormalities or recurrent unexplained stroke. TOE is more likely to identify an atrial abnormality or patent foramen ovale. An i.v. injection of agitated saline can be given to detect right-to-left shunting of blood by visualizing the passage of air bubbles across the patent foramen from right to left atrium during a Valsalva manoeuvre. TOE may also identify ulcerated aortic atherosclerosis or dissection.

Lumbar puncture – for CSF examination, if after CT has excluded distortion of intracranial structures in suspected meningitis or encephalitis. Also to detect blood and xanthochromia in SAH, and to detect increased white cell count and oligoclonal immunoglobulin in those with suspected vasculitis.

Table 41 gives differential diagnosis of vascular causes of stroke.

Table 42 for the localization of site of lesion in stroke.

Management

Acute Ischemic Stroke

1. ***General therapy*** – comprises respiratory and cardiac care, fluid and metabolic management, control of BP, prophylactic measures against DVT, aspiration pneumonia and decubitus ulcer.

Table 41: Differential diagnosis of vascular causes

	Embolism	*Thrombosis*	*Haemorrhage*
1. *Age*	Young	Middle or old	Middle age or old
2. *Nature of onset*	Instantaneous Maximum deficit at onset	Sudden or progressive	Catastrophic Progressive
3. *Premonitory symptoms*	Absent	Difficulty in speaking or weakness of arm or leg may be first symptoms	Usually absent
4. *Common cause*	Mitral stenosis with atrial fibrillation, carotid stenosis	Arteriosclerosis with or without hypertension	Hypertension almost invariable
5. *Clinical features* Headache	Variable	Slight or absent	Severe in large haemorrhage

Contd...

Contd...

	Embolism	*Thrombosis*	*Haemorrhage*
Vomiting at onset	Rare	Rare	Common
Convulsions	Common	Rare	Common
Coma	Rarely deep	Varies with extent of thrombosis	Deep unconsciousness
Cheyne-Stokes respiration or laboured breathing	Not common	Seldom	Common
Stiff neck	Rare	Rare	Frequent
Conjugate deviation of eyes	Rare	Seldom	Frequent
Reaction of pupil to light	No change	May be impaired	Commonly impaired
Blood pressure	Normal	May be high	Usually high
Bilateral extensor plantar	Rare	May be present	Frequent
6. CSF	Usually normal Pleocytosis, if infected embolus	Clear, pressure slightly increased	Usually bloody, pressure increased
7. CT scan or MRI	Infarction may not appear for 24–48 hrs on CT	May not appear for 24–48 hrs on CT scan	Can be confirmed within minutes of onset
8. Termination	Recovery usual	Recovery often	Rapid deterioration High mortality

Note: Large infarct may present like (mimic) bleed, small bleed may present like infarct.

Table 42: Localization of site of lesion

Site of lesion	*Localizing symptoms*
Cortex	F1accid hemiplegia with cortical sensory loss. Aphasia common in dominant hemisphere lesions. Convulsions may occur.
Internal capsule	Commonest site. Hemiplegia. Hemianaesthesia, if lesion in posterior one-third. No loss of consciousness. Spasticity marked.
Thalamus	*Thalamic syndrome* – (i) Fleeting hemiparesis or hemiplegia on the side opposite the lesion. (ii) Impairment of superficial and loss of deep sensation on the opposite side of the body. (iii) Elevation of threshold to cutaneous, tactile, thermal, and painful stimuli, but these when perceived have an abnormal painful quality. (iv) Intolerable, spontaneous pains and hyperpathia on opposite side. (v) Ataxia, tremor and/or choreoathetoid movements on the opposite side. (vi) Conjugate internal deviation of both eyes with weakness of upward gaze, eyes deviated down and medially.
Midbrain	Upper level – Weber's syndrome – 3rd nerve palsy with crossed hemiplegia.
	Lower level – Benedict's syndrome (upper red nucleus syndrome) – 3rd nerve on side of lesion with tremors, hypertonia and ataxia on opposite side.
Pons (Fig. 25)	Millard-Gubler syndrome – Paralysis of lateral rectus, with or without LMN type of facial paralysis on one side with crossed hemiplegia.
	Foville's syndrome – Similar to Millard-Gubler syndrome except that instead of lateral rectus paralysis, there is conjugate ocular deviation to side of lesion.
	Avellis's syndrome – Paralysis of 10th cr. n. on one side (LMN type) with contralateral hemiplegia.
	Horner's syndrome – Paralysis of the ocular sympathetic may result from a lesion in the tegmentum of the pons.
Medulla	Medial medullary syndrome (Dejerine's syndrome) – Ipsilateral flaccid tongue weakness, contralateral hemiplegia and contralateral loss of position and vibration sense (from infarction of medial lemniscus), occasionally upbeat nystagmus.
	Lateral medullary syndrome (Wallenberg's syndrome) – Abrupt onset with vertigo (vestibular nucleus), dysphagia (N. ambiguus), ataxia (inferior cerebellar peduncle). On examination ipsilateral anaesthesia of face (descending tract of 5th nerve), and contralateral of limbs and trunk (spinothalamic tract), ipsilateral Horner's syndrome (descending sympathetic fibres), nystagmus (vestibular nerve and cerebellar fibres), ipsilateral intention tremor (inferior cerebellar peduncle).

Contd...

Contd...

Site of lesion	*Localizing symptoms*
Temporal lobe	Deep posterior temporal lobe – Pyramidal fibres pass in close proximity to visual fibres hence hemiplegia usually associated with homonymous hemianopia or upper quadrantic field defect.
	Anterior temporal lobe – On the dominant hemisphere the pyramidal system lies just medial to the speech fibres, hence hemiparesis associated with expressive aphasia.
Spinal cord	Unilateral lesion of the corticospinal tract below the medulla and fifth cervical segment produces spinal hemiplegia involving the limbs of the affected side but without paralysis of muscles innervated by cranial nerves.
Cerebellum (Figs. 26 and 27)	Acute cerebellar infarct is due to vertebrobasilar ischemia and presents with severe vomiting, headache, vertigo and altered sensorium. Being in the posterior fossa, it can deteriorate fast and herniate.

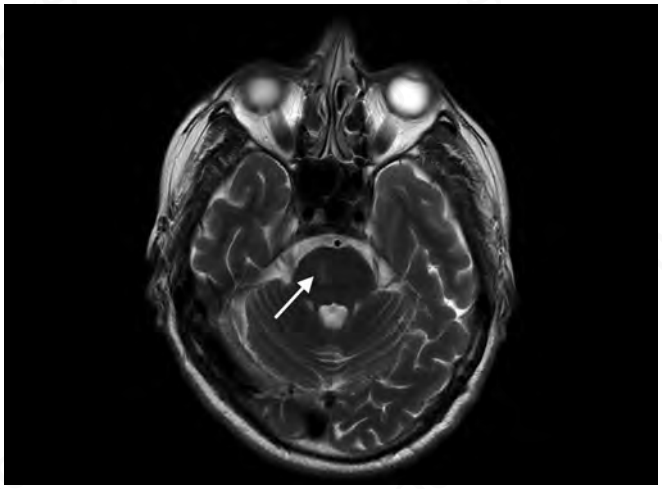


Fig. 25: Acute infarct in pons MRI axial view T2 image

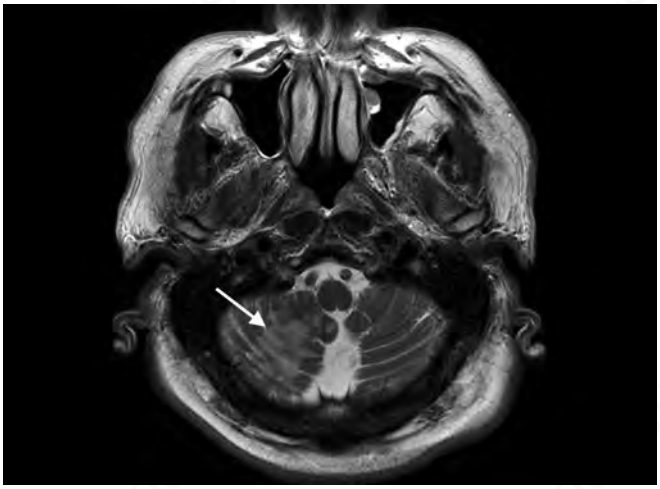


Fig. 26: Cerebellar infarct MRI axial view T2 image

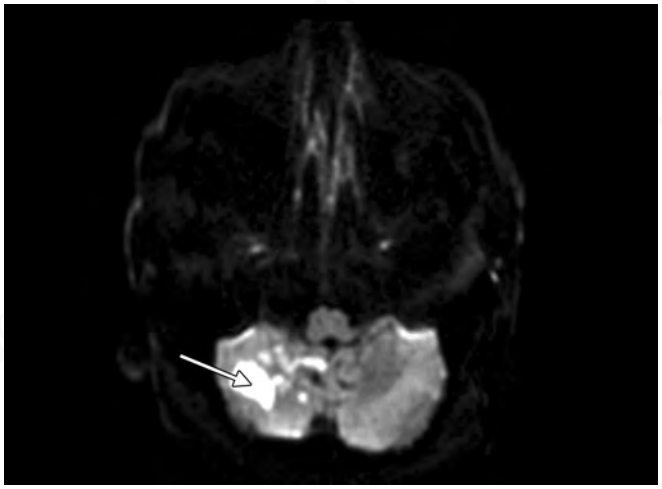


Fig. 27: Cerebellar infarct MRI DW image

(a) *Oxygen* – 2–4 litres/minute nasally helps attain adequate oxygenation of the penumbra. Intubation should be considered in case of vertebrobasilar and hemispheric infarction and also in cases of pathological respiratory pattern.

(b) *Assessment of cardiac function* includes optimal cardiac output, maintenance of high normal BP and a normal heart rate. Cerebral blood flow autoregulation depends on Mean Arterial Pressure, hence a drop in BP should be prevented to maintain optimum cerebral perfusion. As a result, BP level of 180/100 should be maintained in previously hypertensive patient. In other cases mild hypertension is desirable.

(c) *Blood sugar* – above 100 mmol/L should be managed with insulin titration.

(d) *Fever* – Temp. >37.5°C should be treated with paracetamol. Also the cause of the fever should be ascertained and treated appropriately.

(e) *Fluid and electrolytes* should be monitored.

2. ***Specific therapy*** – (a) Thrombolysis with recombinant-tissue plasma activator (rT-PA) 0.9 mg/kg administered within 3 hours of acute ischemic stroke with 10% as bolus and remainder of the drug by infusion over one hour. Table 43 for the eligibility criteria for iv rT-PA for acute ischemic stroke.

Table 43: Eligibility criteria for iv rT-PA for acute ischemic stroke
Inclusion criteria
• Onset of symptoms to drug administration time <4.5 hours.
• Clinical diagnosis of stroke
• No hemorrhage on CT scan or edema of > 1 /3 of the MCA territory
• Age >18 years
• Consent by patient or surrogate
Exclusion criteria
• Stroke or severe head trauma in last 3 months or prior intracranial hemorrhage
• Major surgery in last 14 days
• Systolic BP above 185 or Diastolic >110.
• If patient is rapidly improving or has minor symptoms
• Symptoms suggest SAH
• Haematuria, malena, haemoptysis or GI bleeding within last 21 days
• Seizure at onset of stroke
• Elevated PTT, use of heparin in last 48 hours
• Prothrombin time >5 sec.
• Platelet count <100,000/mm^3
• Glucose <50 or >400 mg/dL
• Recent myocardial infarction
• Coma or stupor

In patient with stroke onset <8 hours with occlusion of major carotid artery (MCA), intraarterial thrombolysis can be considered after DSA. Mechanical removal of clot using devices like MERCI device or stent, retrievers can be attempted.

3. ***Prevention of complications*** – (a) Nasogastric tube significantly reduces risk of post-stroke pneumonia by preventing aspiration. (b) Treatment of urinary tract infection if any. (c) Prevention of DVT and pulmonary embolism – Physical therapy, support stockings and LMW heparin. (d) Prevention of decubitus ulcer by frequent change of position in bed. (e) Treatment of brain oedema with mannitol. (f) Decompressive surgery for MCA infarction allows extracranial expansion of the oedematous brain tissue to avoid ventricular compression and may be lifesaving at times.
4. ***Rehabilitation*** should be active, based on the degree of disability. (a) Active physiotherapy protects against DVT. Prevention of DVT and pulmonary embolism among bedridden patients is the only indication for early anticoagulation after acute ischemic stroke. (b) Aspirin given early may be considered in all patients mainly to reduce the risk of early recurrence. (c) Treatment of aphasia – Language training of left hand in performance of voluntary movement, in right handed patients.

INTRACEREBRAL HEMORRHAGE

Blood pressure

- Mean arterial pressure <130 in those with history of hypertension
- Avoid mean arterial pressure <110, if patient is post-operative
- Prevent fall of systolic BP <90

Intracranial pressure

- No steroids are indicated
- Intracranial therapy is defined more than 20 mm Hg for > 5 min.
- Maintain cerebral perfusion pressure >70 mm Hg
- Osmotherapy – Mannitol 20% 0.25–0.5 g/kg every 4 hour, keeping sodium osmolality goal of ≤310 mOsm/decilitre
- Hyperventilation – $PaCO_2$ 30–35
- Muscle relaxants
- Non depolarizing neuromuscular blockade
- Maintain euvolaemia

Temperature

- Treat temp. > 38.5°C

Medical therapy

- Factor rVII given within 4 hours after intracerebral hemorrhage

Surgery – Posterior fossa craniotomy in cases of cerebellar hemorrhage or infarction with acute obstructive hydrocephalus. Ventricular decompression with external ventricular drainage also can reduce intracranial pressure.

Secondary prevention

1. General measures – Stopping smoking, regular exercise. Control of hypertension, diabetes and treatment of hyperlipidemia.
2. Antiplatelet agents – Combination of Prasugrel 5 mg bd, or Ticagrelor 90 mg bd along with low dose Aspirin 25 mg bd is more effective than Aspirin alone in TIA or ischemic stroke. Combination of Aspirin and Clopidogrel 75 mg/day have been used but with increased risk of bleeding.

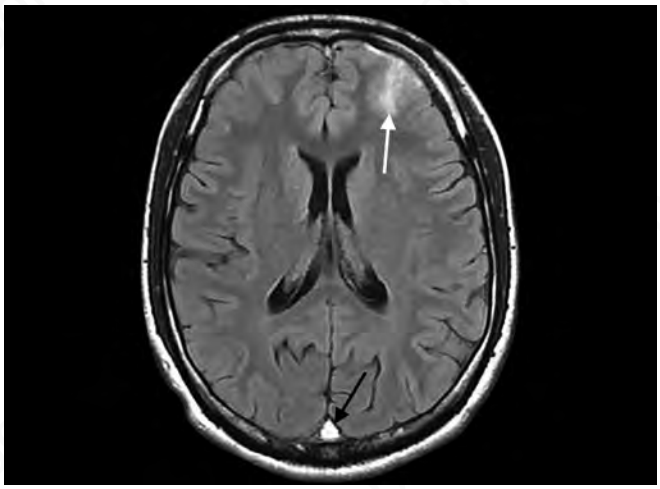


Fig. 28: Superior sagittal sinus thromobosis with loss of flow void (black arrow) with venous infarct (white arrow)

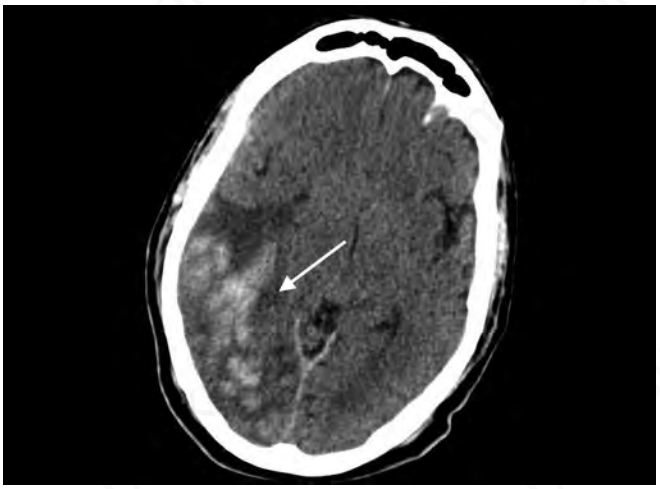


Fig. 29: Sinus thrombosis with venous infarct (arrow)

3. Preventive neurosurgery – For recurrent subarachnoid and intracerebral bleeding from aneurysms and arterial malformations. In acute cerebellar infarction, if impending herniation, posterior fossa surgical decompression.
4. Carotid artery stenosis – (i) ***Carotid endarterectomy*** – *Indications* – (a) Moderate degree of stenosis. (b) TIA, amaurosis fugax, stroke or retinal infarct within 6 months and with good recovery. (c) Significant stenosis in patient scheduled for major surgery such as coronary bypass.

   (ii) ***Percutaneous transluminal angioplasty*** with stenting is an alternative treatment.

   Contraindications – (a) Recent MI. (b) CHF. (c) Uncontrolled hypertension. (d) Age over 80 years.

VENOUS INFARCTION

Thrombosis of cortical veins and/or dural sinuses is less common than central arterial occlusion.

Causes – Dehydration, pyogenic middle ear or sinus infection, pregnancy and puerperium, polycythemia, hyperviscosity syndromes, septicaemia, ulcerative colitis, severe iron deficiency anaemia, head injury, extracranial malignancy, oral contraceptives.

Clinical features – Onset is sudden commonly with focal epilepsy. Raised intracranial pressure develops rapidly if obstruction of the dural sinuses. A focal neurological deficit develops which can be clinically indistinguishable from a stroke due to arterial occlusion, severe headache, papilloedema.

Table 44: Predisposing causes of cerebral aneurysms

1. Coarctation of aorta.
2. Polycystic kidney disease.
3. Renal artery stenosis (fibromuscular dysplasia).
4. Essential hypertension.
5. Ehlers-Danlos syndrome type IV.
6. PAN.
7. SLE.
8. Wegener's granulomatosis.

Investigations – An enhanced CT scan may show a clot within the superior sagittal sinus, but this is better demonstrated by MRI (Figs. 28 and 29). Angiography may be required to make a definite diagnosis.

Treatment – (a) Antibiotics – if sinus thrombosis is infective in origin. (b) IV low molecular weight dextran. (b) Anticoagulants – recommended in spite of presence of haemorrhagic component of the infarct since the underlying cause is thrombosis of the venous sinuses.

Local thrombolysis of the sinuses in case of severe sinus occlusion and raised IP and unconscious patient.

SUBARACHNOID HAEMORRHAGE (SAH)

Causes

1. Intracranial aneurysm – Rupture of congenital berry aneurysm or angioma. In order of frequency the aneurysms arise from anterior cerebral arteries, internal carotid intracerebrally, middle cerebral and from the basilar system. Rarely rupture of a mycotic aneurysm (Table 44).

2. Arteriovenous malformation.
3. Cerebral or cerebellar haemorrhage leading into the ventricles or subarachnoid space.
4. Trauma.
5. No obvious cause.

Mycotic aneurysm more often causesdistal bleed, not SAH.

SUBARACHNOID HEMORRHAGE

Two common sites are proximal portions of anterior communicating artery and at the origin of posterior communicating artery from the stem of the internal carotid.

SPONTANEOUS SUBARACHNOID HAEMORRHAGE

Clinical Features

1. **Before rupture** – In some cases of aneurysm. Migraine, focal symptoms like transitory attacks of blindness, monoplegia, cranial nerve palsies, or trigeminal anaesthesia.
2. **After rupture**
   - *Symptoms due to rapidly increasing intracranial pressure with meningeal irritation* – The intensity of symptoms depends on rapidity and persistence of hemorrhage. Loss of consciousness with generalized flaccidity occurs when leakage is considerable. In less severe cases the patient may remain semi-stuporose with severe headache and signs of meningeal irritation – headache, photophobia, neck stiffness and Kernig's sign.

     Fever – Moderate pyrexia common. If severe and fluctuating, it may suggest ischemic hypothalamic damage.

     Fundus – Unilateral or bilateral haemorrhages in some cases, may be accompanied by subhyaloid and vitreous haemorrhages.
   - *Focal symptoms* – due to compression of neighbouring cranial nerves by blood clot, or to invasion of the cerebral hemisphere by the hemorrhage – (i) Visual field defect from compression of optic nerve, chiasma or tracts. (ii) 3rd, 4th and 6th nerve involvement, if aneurysm near cavernous sinus. (iii) Mental impairment, hemiparesis, and if on left side expressive aphasia from hemorrhage from aneurysm at junction of anterior cerebral and anterior communicating arteries invading the frontal lobe. (iv) Epileptiform convulsions and monoplegia if leakage of aneurysm in cortical course of middle cerebral. (v) Crossed homonymous hemianopia due to hemorrhage into substance of posterior lobe. (vi) Quadriplegia or crossed paralysis, if basilar artery aneurysm and leakage. (vii) Head retraction, if bleeding into posterior fossa.
   - *Reactive hypertension* – Rise of BP in patients with no evidence of pre-existing hypertension may take several days to return to normal.

Complications: of Aneurysmal SAH

A. Intracranial

1. *Rebleeding* – Risk of recurrent hemorrhage reaches its peak between 10th and 14th day after initial rupture. About 30% rebleed.
2. *Cerebral ischemia* – A blood clot in subarachnoid space in vicinity of major cerebral vessels may result in development of cerebral arterial spasm after 5–10 days. Diagnostic features – (a) Gradual fall in level of consciousness. (b) Appearance or worsening of focal neurological deficits such as dysphasia or hemiplegia. (c) Repeat lumbar puncture shows no evidence of fresh hemorrhage and (d) CT scan – In patients with focal signs there are usually areas of ischemia which do not show characteristic wedge-shaped patterns of arterial infarction and are often haemorrhagic.
3. *Hydrocephalus* – may develop some weeks after SAH and should be considered in patients who fail to improve. CSF drainage may be impaired by blood clot within basal cisterns or obstruction of arachnoid villi ('communicating' hydrocephalus), or blood clot within ventricular system ('obstructive' hydrocephalus).
4. *Expanding intracerebral hematoma* – Brain swelling around the hematoma may cause progressive deterioration in level of consciousness or progression of focal signs.
5. *Seizures* – generalized or focal may occur at any stage especially if cortical damage from the hematoma.
6. Hyponatremia – there is natiuresis and volume depletion, seen immediately within 2 hours (cerebral salt wasting syndrome)

B. Extracranial

1. *Cardiac* – Myocardial infarction and cardiac arrhythmias due to catecholamine release following ischemic damage to hypothalamus.
2. *Pulmonary oedema* – Probably as a result of massive sympathetic discharge.
3. *Gastric hemorrhage* – from stress erosions.
4. *SIADH.*

Investigations

CSF – Pressure raised, red cells with supernatant fluid xanthochromic. Proteins increased slightly and mononuclear pleocytosis usually due to irritation of meninges by extravasated blood.

Angiography – may reveal the causal lesion in about two-third cases. It should be done unless the patient's condition contraindicates surgery because of shock, old age, atheroma of severe degree or hypertension, even if the lesion is demonstrated.

Skull radiograph – Shift of pineal gland (if calcified) when there is a large hematoma.

CT scan – (a) Confirms diagnosis of SAH. (b) Identifies other associated lesions such as hydrocephalus, intracerebral hematoma, A-V malformation. (c) Helps identification of site of aneurysm rupture.

Digital subtraction angiography – has the advantage of giving computer-enhanced images and amount of contrast material required is small (Fig. 30).

Prognosis: About one-third die in first attack; of survivors about half have recurrence within 2–4 weeks. Tendency for interval between successive haemorrhages to become shorter. Prognosis better with angioma than with aneurysm.

Management

1. Medical – (a) *General* – Bed rest with head slightly elevated. If an aneurysm has been demonstrated and patient is not suitable for surgery, a minimum of 4 weeks of complete rest in bed will probably reduce risk of recurrent hemorrhage. (b) *Reduction of BP* – towards normal unless there is evidence of progressive neurologic deficit due to ischemia. (c) *Nimodipine* – A calcium channel blocker reduces the incidence of cerebral ischemia. Dose 60 mg every 4 hours should be started as soon as possible and continued for 21 days after the SAH. (d) Reduction of increased intracranial pressure as indicated by headache, convulsions or stiff neck. Spinal puncture is done only for diagnostic purposes. Repeated lumbar punctures may give rise to a new leakage. (e) *Symptomatic treatment* – Analgesics and/or diazepam for headache and restlessness.
2. Surgical – for prevention of rebleeding– (a) *Direct clipping* – of the aneurysm neck – is optimal method of treatment. (b) *Trapping* – Clipping of proximal and distal vessels for giant aneurysms and intracavernous aneurysms. Prior anastomosis of superficial temporal to middle cerebral artery minimises the risk of ischemic deficit. (c) *Wrapping* – If clipping is not possible because of the width of the aneurysm or its attachment to adjacent vessels, muslin gauze can be wrapped round the fundus. (d) *Induced thrombosis* – within the aneurysm sac. Risky and rebleeding may occur. (e) *An aneurysm is localized* – Ligation of internal carotid or common carotid artery in neck. Indications – (i) Young patients with severe initial hemorrhage or early recurrences. (ii) Subdural hematoma following ruptured aneurysm. (iii) Aneurysms arising directly from carotid artery where clipping has failed or not attempted, e.g. intracavernous or giant ophthalmic artery aneurysm. (f) *Coiling* - Endovascular techniques involve placing platinum coils or other embolic material, within the aneurysm via a catheter that is passed from the femoral artery.
3. *After recovery* – Metabolic changes due to release of catecholamines produce ischemia of hypothalamus, kidneys and heart. Hence glycosuria, high blood pressure, ECG changes. Vascular spasm may produce drowsiness, confusion, hemiplegia and aphasia.

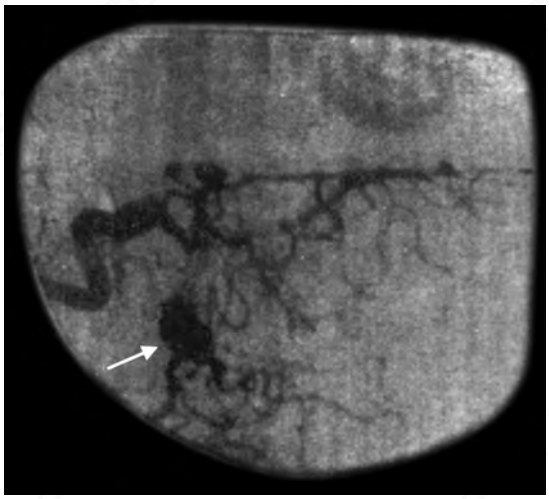


Fig. 30: IV DSA image of the left carotid artery shows a large aneurysm arising from the left middle cerebral artery (arrow)

ARTERIOVENOUS MALFORMATIONS (AVMs)

AVMs are congenital abnormalities which may affect any part of the brain, including cerebellum and brainstem.

Clinical Presentation

1. Intracranial bleeding – more commonly intracerebral.
2. Epilepsy – AVMs responsible are usually large parietal lesions.
3. Progressive neurological deficits – such as slowly evolving hemiparesis.

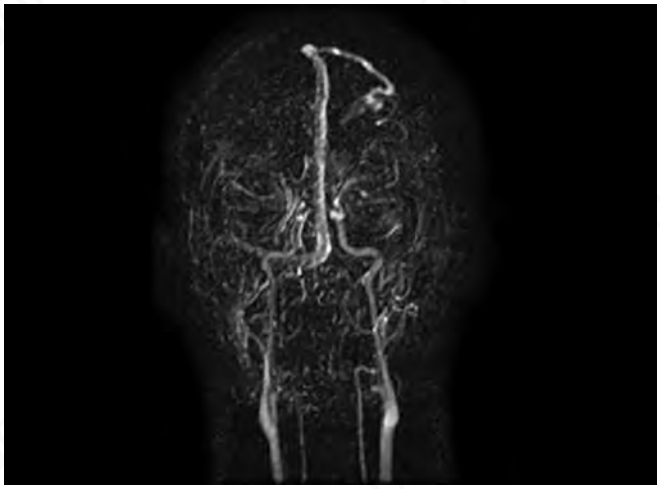


Fig. 31: AV malformation dynamic post-contrast early filling of superior sagittal sinus

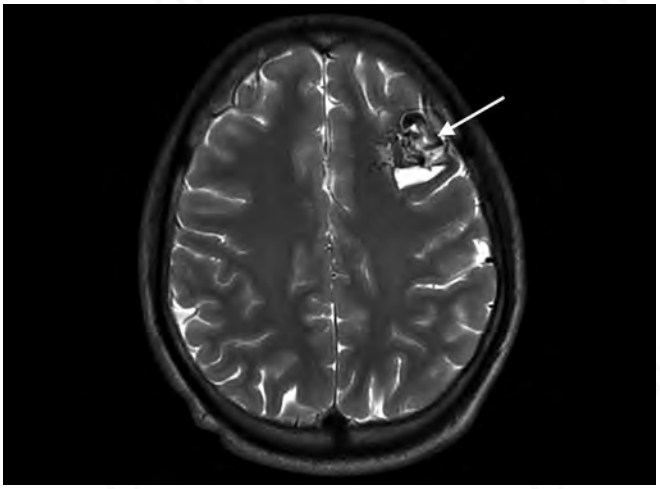


Fig. 32: AV malformation flow voids in MRI T2 image

4. Headache – may be the only presenting symptom. Migraine like headache in occipital AVM.

Investigations – CT scan can demonstrate large AVMs. Angiography for small AVMs when surgical excision is being considered (Figs. 31 and 32).

Treatment – (a) Surgery indicated if hemorrhage has occurred and the malformation is easily accessible and can be excised without neurological deficit. (b) Embolization of feeding arteries of large lesions with multiple feeders. (c) Stereotaxic radiosurgery may be used to obliterate small AVMs.

13. COMA AND BRAINSTEM DEATH

Coma is a state of total absence of awareness of self and environment. Unconsciousness may result from disturbances (functional or structural) of large areas of both cerebral hemispheres and/or upper brainstem structures. Table 45 for the causes of coma.

Table 45: Causes of coma

1. Structural brain damage (supratentorial, infratentorial):
   - Infarction
   - Haemorrhage
   - Head injury
   - Tumour
   - Haematoma
   - Infection: meningitis, cerebral malaria, encephalitis, abscess
   - Brainstem demyelination (multifocal, diffuse, metabolic disease)
2. Systemic causes:
   - *Metabolic* – Anoxia-ischemia. Respiratory, cardiac, hepatic diseases or kidney failure. Hypoglycemia. Wernicke's encephalopathy. Hypo/hypernatremia, Hypo/hypercalcaemia.
   - *Endocrine* – Diabetic coma, myxoedema, Addison's disease, pituitary apoplexy.
   - *Drug overdose and poisons* – Barbiturates, organophosphorus poisoning, alcohol, carbon monoxide poisoning, etc.
   - *Physical agents* – Hypothermia, heat stroke.
   - *Hypertensive encephalopathy*.
   - *Septicaemia.*
3. Psychogenic

DIAGNOSIS OF COMA

Structural Brain Damage

A. **Supratentorial mass lesions:**

1. *Signs of causative lesion* – e.g. hemiparesis, papilloedema.
2. *Signs due to expanding mass lesion* – causing downward displacement of the temporal lobe over the edge of the tentorium (uncal herniation), or midline compression of the upper brainstem – (a) *Uncal herniation* – Signs of hemiparesis and papilloedema, and sequential loss of 3rd nerve function. Unilateral dilatation of the pupil with impaired response to light implies temporal lobe herniation. (b) *Central herniation* – Orderly progression of brainstem dysfunction – (i) At first reactive small pupils and Cheyne-Stokes respiration are present and the patient can be roused by painful stimuli. (ii) Midbrain compression causes decerebrate rigidity, dysconjugate eye movements and fixed medium-sized pupils and the subject is

then virtually unresponsive. (iii) Finally the pupils dilate, respiration becomes grossly irregular, no eye movements can be elicited and patient is deeply comatose. Medullary involvement causes gasping, usually a terminal sign. (c) *Cerebellar herniation* (see later).

B. **Brainstem (local) lesion:**

1. *Rapid onset of coma* – Infarction of brainstem.
2. *Abnormalities of pupil responses and eye movements* – Present from the onset and orderly sequence of changes caused by herniation is not seen. Pupils may be fixed and counter rolling of head may reveal dysconjugate eye movements and loss of gaze in one direction. Pontine haemorrhage produces pin point pupils, loss of eye movements and hyperthermia. The eyes look toward a hemispheral lesion and away from a brainstem lesion.
3. *Cranial nerve signs.*
4. *Bilateral long tract sings.*

Metabolic Coma

1. Absence of signs of focal lesion in CNS (except in hypoglycemia) like hemiplegia, 3rd nerve palsy.
2. Preserved pupillary responses (except in cases of anoxia and glutethimide poisoning).
3. Retained eye movements. Dolls eye movement absent.
4. Symmetrical, hypotonic limbs with depressed reflexes.
5. Depressed or Cheyne-Stokes respiration.
6. Flapping tremor, generalized myoclonus, muscle twitching, and acidotic respiration – may be seen in some metabolic causes, e.g. hepatic or respiratory failure, delirium precedes deterioration in consciousness.

INVESTIGATION OF A CASE OF COMA

History

1. *Mode of onset* – Abrupt loss of consciousness in cerebrovascular accidents and postictal, rapid and in a period of few hours in some cases of intracranial hemorrhage and some toxic states; gradual over days in expanding intracranial lesions, metabolic or infective cause.
2. *Premonitory symptoms* – Complete absence of premonitory symptoms would suggest a primary intracranial vascular accident.
3. *Headache* – with vomiting, progressive mental changes, increasing weakness or unsteadiness of limbs would suggest an expanding intracranial lesion. Severe headache and vomiting at onset with immediate loss of consciousness in hypertensive patient favours diagnosis of intracerebral hemorrhage. History of fever with headache and vomiting in meningitis, meningoencephalitis with or without hydrocephalus.
4. *History of severe psychological disturbance* – raises possibility of self-administered drug intoxication.
5. *History of alcohol intake.*
6. *History of head injury* – (i) On admission – Diffuse shearing injury and/or intracranial hematoma. (ii) Previous head injury (e.g. 6 weeks) – Chronic subdural hematoma.
7. *History of bleeding diathesis* – Non-traumatic intracerebral hemorrhage is usually associated with systemic hypertension but may occur in patients with bleeding diathesis.
8. *Recent symptoms suggestive of a tumour* – e.g. headache, personality change or insidious hemiparesis.
9. *Symptoms of cerebellar hemorrhage* – Headache, vertigo and vomiting, with unilateral cerebellar ataxia, would suggest occurrence of hemorrhage into one cerebellar hemisphere.
10. *Past history* – Of diabetes mellitus, epilepsy (post-ictal state), kidney disease, cardiac or respiratory failure or of hypertension or malignancy (intracranial metastasis). Previous overdose attempts due to depressive illness.

General Examination

1. *General appearance* – Flushed face in alcoholic, pale yellow in uraemia, cherry red in carbon monoxide poisoning. Cold clammy skin suggests hyperinsulinism or morphine poisoning; pigmentation of skin and buccal mucosa in Addison's disease; petechiae in skin suggestive of cerebral embolism.

   Fever – usually indicates a systemic infection, meningitis, cerebral malaria, encephalitis or cerebral abscess.
2. *Odour* – of alcohol, sweet smell in diabetic ketosis, ammoniacal in uraemia, and of drug like cyanide. Foetor hepaticus in hepatic coma. Pungent odour in organophosphorous poisoning.
3. *Head* – Depressed fracture of skull may be palpable.
4. *Ears* – Blood may suggest basal fracture. Middle ear infection or tenderness and swelling over mastoid may indicate an intracranial abscess.

5. *Eyes* – (a) *Jaundice* in liver failure. (b) *Soft eyeballs* in diabetic acidosis. (c) *Resistance to opening of eyes* and rolling up of eye balls in hysterical coma.
6. *Hypothermia* – following exposure to low temperatures, intoxication with alcohol or hypnotics, profound myxoedema or peripheral circulatory failure, barbiturate poisoning.
7. *Tachy or bradyarrhythmias* or evidence of valvular heart disease or peripheral emboli suggest cardiogenic cause. Bruits over carotids suggest cerebrovascular disease (Embolic stroke).
8. *Hypotension* – Possibility of shock, myocardial infarction or septicaemia or Addison's disease, barbiturate poisoning.
9. *Respiration* – Slow, shallow breathing suggests drug intoxication. Deep and rapid respirations suggest pneumonia or metabolic acidosis or diabetic ketosis. Periodic respiration suggests cardiac or brainstem lesion.
10. *Enlargement of an abdominal organ* – might indicate portal hypertension, polycystic kidneys and an associated SAH.
11. *Purpura* – suggests a bleeding diathesis, and bruising around the head possible trauma or fracture at base of skull.
12. *Rash* – may indicate an infective or inflammatory disease, meningococcal meningitis.
13. *Evidence of puncture wounds* – may identify a diabetic patient or a drug user.

Neurological Examination

Glasgow coma scale – The patient's response to certain stimuli (supraorbital pressure, rubbing the sternum with knuckles. pressing the side of a pencil on the nail-bed, and pressure on Achilles tendons) is observed (Table 46).

Table 46: Glasgow coma scale

Maximum score = 15, minimum = 3		
		Score
Eye	*Spontaneous*	4
opening:	To speech	3
	To pain stimulus	2
	Nil	1
Verbal	Orientated	5
response:	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	Nil	1
Motor	Obeys commands	6
response:	Localizes pain	5
(best limb)	Withdraws	4
	Abnormal flexion to pain	3
	Extension to pain	2
	Nil	1

Brainstem Function

Pupils

- Unilateral dilatation of pupil with no light response suggests an uncal herniation; expanding supratentorial lesion it may also be seen in posterior communicating artery aneurysm or other IIIrd nerve damage.
- Mid-brain lesions typically cause loss of light reflex with pupils in mid-position, and lesions in the pons cause miosis with retained light responses.
- Fixed dilatation of pupils suggests significant brainstem damage, but must be differentiated from the fixed dilatation from earlier instillation of atropine-like agents.
- Horner's syndrome may be seen with lesions in the hypothalamus or brainstem, but can also be observed in diseases affecting the wall of the carotid artery.
- Small pupils which are reactive – metabolic coma, diencephalic lesion. Pinpoint and reacting – pontine lesions (requires magnifying lens to examine light response). Drug intoxication tends not to affect pupillary light responses. Opiates and organophosphorus poisoning cause bilateral pinpoint pupils.
- Anaesthesia results in unreactive and slightly dilated pupils.

Corneal response – is usually retained until very deep coma. If it is absent in patient in light coma, the cause of coma may be drug intoxication. Loss of corneal reflex in absence of drug overdosage is a poor prognostic indicator. Suggests brainstem (pons) dysfunction.

Spontaneous eye movements – (a) Conjugate deviation of the eyes suggests a focal hemispheric or brainstem lesion. (b) Depression of eye movements may occur in midbrain damage at level of the tectum and occasionally in metabolic coma. (c) Skew deviation suggests a lesion at pontomedullary junction. (d) Dysconjugate eyes suggest damage to oculomotor or abducens nerve in brainstem or pathways. Repetitive conjugate horizontal ocular

deviation ('ping-pong gaze') is an indicator of brainstem lesions. Nystagmus, in which the eyes jerk backwards in the orbits, usually indicates a mid-brain lesion. Irritative or epileptic phenomenon cause deviation of eyes away from a cerebral lesion. Conversion retraction nystagmus – Dorsal brain lesion (Parinaud's syndrome). In pontine lesions eyes are deviated away from the lesion. Eyes are deviated downwards and medially in lesions due to compression on midbrain tectum. Wrong way eyes (deviation away from lesion) may be seen in medial thalamic lesions. Intermittent jerking downwards of the eyes (ocular bobbing) is seen with lesions in the low pons.

Reflex eye movements – (a) Oculocephalic response is tested by rotating the patient's head from side to side and observing the position of the eyes. With intact brainstem activity, the eyes move conjugately in a direction opposite to the head movements (*doll's eye movements*), but when the brainstem is depressed the eyes remain in the mid-position of the head. (b) Oculovestibular testing involves instilling 50 mL of ice cold water into the ear. Conscious patients, or those with psychogenic coma, will develop nystagmus with the quick phase away from the side of the stimulation. A tonic response with conjugate movements of the eyes towards the stimulated side indicates an intact pons and suggests a supratentorial cause for the coma; a dysconjugate response or absence of response, implies a lesion in the brainstem.

Respiratory pattern – Long-cycle Cheyne-Stokes respiration indicates damage at the level of the diencephalon, and short-cycle occurs with damage at medullary level. Central neurogenic hyperventilation occurs with lesions in the low mid-brain and upper pons. Reflex responses such as yawning, vomiting and hiccough may occur with brainstem disturbance. Acidotic respiration suggests diabetic ketoacidosis or uraemia.

Motor function – is assessed for the Glasgow coma scale, but lateralizing abnormalities are important. (a) Generalized or focal seizures implies hemispheric damage and may help lateralization. (b) Multifocal myoclonus favours a metabolic or anoxic cause for coma with diffuse cortical irritation. (c) Tendon reflexes – Deep tendon reflexes and plantar response may also give clues to lateralization, implying a focal cause for coma, though focal signs may be seen in hepatic encephalopathy and hypoglycemia.

Involuntary movements – (a) Asterixis, tremulousness and multiple myoclonic jerks are usually seen in patients with metabolic encephalopathies. (b) Multifocal seizures may also occur in patients with uraemia and hyperglycaemic hyperosmolar state (HHS).

Spleen – may be palpable in cerebral malaria.

Pulse – Slow, full bounding pulse suggests increased intracranial pressure. Slow in morphine poisoning, brain tumour and Stokes-Adams syndrome. Irregular pulse may be found in valvular heart disease causing embolism.

Fever – in cerebral malaria, subarachnoid, intracerebral or pontine haemorrhage; sun stroke, septicaemia. May be normal in morphine poisoning and uraemia.

Sweating – strikingly absent in heat hyperpyrexia.

Blood pressure – elevated in uraemia or cerebral haemorrhage.

Fundus – Papilloedema in intracranial tumour, cerebral venous sinus thrombosis or hypertensive encephalopathy; white patches and haemorrhages in uraemia, changes of diabetic retinopathy, subhyaloid haemorrhage in SAH.

Laboratory Investigations

1. *Urine* – for sugar, albumin and acetone for toxic screening (benzodiazepines, alcohol).
2. *Blood* – Blood count, estimation of blood glucose, electrolyte values including calcium. Blood urea. Blood levels of common intoxicants. Blood ketones and osmolality in certain circumstances. Blood smear for malarial parasites. Blood culture.
3. *CSF* – for evidence of haemorrhage, meningitis or encephalitis. (Lumbar puncture may be deferred, if a mass lesion is present.)
4. *Analysis of vomit or gastric lavage.*

Radiography

1. *Of skull* – to demonstrate any fracture, to show condition of sella – erosion would suggest increased intracranial pressure; to show infection in sinuses, mastoids or petrous bones which may suggest intracranial infection; to demonstrate pineal shift which suggests a mass lesion.
2. *Of chest* – may reveal carcinoma (cerebral metastasis), bronchiectasis, abscess or empyema (cerebral abscess), tuberculosis (meningitis) or mitral stenosis (cerebral embolism).

CT Scan or MRI

(a) Coma with focal signs or evidence of head injury, whether the focal signs indicate a brainstem or supratentorial lesion. A normal scan may be seen in patients with hypoglycemia or hepatic coma.

(b) Coma without focal signs but with meningeal irritation – Brain imaging to identify subarachnoid blood excludes the focal collections in case of bleeding or infection. Depending on the results of the scan a lumbar puncture can be undertaken.

(c) Coma without focal or lateralizing neurological signs without meningismus – Most of these patients have suffered diffuse anoxic or ischemic disease, e.g. following cardiac arrest. Metabolic derangement or drug insult. Imaging may be necessary, but assessment of metabolic indices and toxic metabolites in the blood will provide the diagnosis. LP may be indicated to exclude an inflammatory or infective cause. Marked depression of brainstem responses in a patient who appears to be in relatively light coma suggests drug-induced coma.

Cerebral Angiography

Useful aid in brain tumour and subdural haematoma.

EEG

(a) In comatose patients, where clinical examination has failed to localize the lesion, an EEG may localize it to one hemisphere, of particular value in cerebral abscess. (b) May provide evidence of nonconvulsive status. Triphasic waves in hepatic encephalopathy, uraemia, periodic lateralizing discharges in herpes encephalitis. Burst suppression in hypoxic - ischemic encephalopathy. Normal EEG may suggest locked-in state. Isoelectric, flat EEG (< 2 mV amplitude) suggests brain death (Electrocerebral silence, inactivity). Alpha coma waves anteriorly seen in drug-induced coma, post hypoxic. (c) An entirely normal EEG will make a supratentorial lesion unlikely. (d) It may give evidence of a specific cause such as hepatic encephalopathy or herpes simplex encephalitis, or minor epileptic status.

Therapeutic test

IV 50% glucose can be given as a therapeutic test in any case of unexplained coma or hemiparesis where hypoglycemia is suspected (oral hypoglycaemic induced, self-medication with insulin).

DIFFERENTIAL DIAGNOSIS OF COMA

Vascular Causes

1. *Cerebral haemorrhage, thrombosis or embolism* – (Refer).
2. *Subarachnoid haemorrhage* – (i) Sudden intense headache. (ii) Meningeal signs and neck rigidity usually prominent. (iii) Focal neurological signs frequently absent but can occur and are usually due to intracerebral clot or infarction in the region of the involved territory. (iv) Subhyaloid haemorrhage may be noted on fundus examination. (v) CSF – presence of blood.
3. *Hypertensive encephalopathy* – (i) Common in patients with acute hypertension as in eclampsia, pheochromocytoma or acute GN. (ii) Convulsions, either focal or generalized. (iii) Transient cerebral symptoms like blindness, aphasia or hemiplegia. (iv) Papilloedema. (v) Lumbar puncture – CSF gushes out in a stream (raised intracranial pressure).
4. *Cerebral venous thrombosis* – Superior longitudinal sinus thrombosis (Figs. 33 and 34) occurs in relation to extra and intracranial sepsis, debilitating diseases, dehydration, pregnancy, post-partum period,

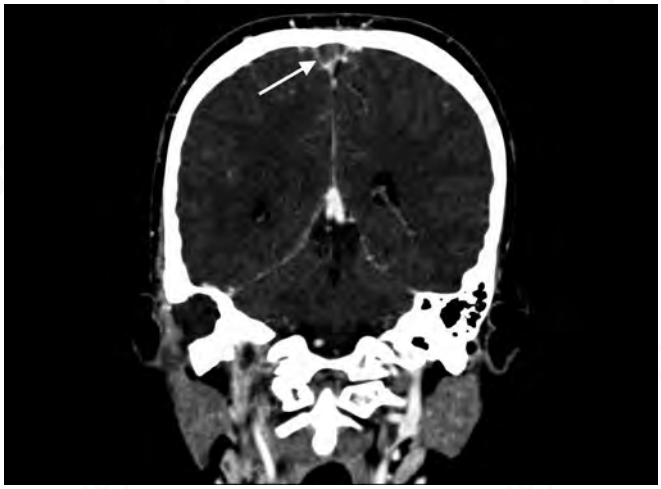


Fig. 33: CT venography shows superior sagittal sinus thrombosis empty delta sign (arrow)

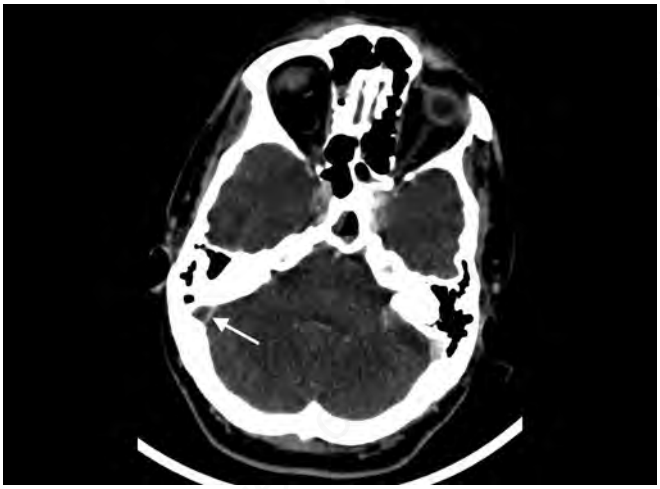


Fig. 34: CT venography shows filling defect in right sigmoid sinus due to thrombosis (arrow)

polycythemia, or in women taking contraceptive pills. Common clinical features include focal seizures, loss of sensation and movement in the legs (crural dominance), and features of raised intracranial pressure – headache, vomiting and papilloedema.

5. *Adams-Stokes syndrome* – (i) History of myocardial infarction. (ii) Giddiness, faintness and convulsions precede coma. (iii) Heart rate very slow.
6. *Shock* – due to injury or loss of blood. (i) Evidence of cause. (ii) Low blood pressure. (iii) Feeble pulse. (iv) Cold and clammy skin.

Metabolic Disorders

Relative preservation of brainstem reflexes. Seizures. Symmetrical signs. No focal findings.

1. *Diabetic coma* (Hyperglycaemic ketoacidosis) – History of diabetes. Dehydration and hyperventilation (Kussmaul's respiration). Breath smells of acetone. Often hypotension, tachycardia, warm skin.
2. *Chronic kidney failure* (Uraemia) – History of renal disease. Variable rate of progress. Anaemia, hypertension. Ammoniacal odour of breath. Raised blood urea and creatinine.
3. *Hepatic coma* – (i) Preceding stage of acute hepatitis or cirrhosis. (ii) Severe jaundice. (iii) Liver may be palpable. (iv) Vomiting. (v) Headache, delirium or convulsions. (vi) Hepatic foetor usually present when collateral vessels link portal (gut) with systemic (mouth) circulation.
4. *Hypoglycaemic coma* – (i) History of taking insulin or spontaneous (insulinoma). (ii) Sudden onset. (iii) Headache common. (iv) Diplopia, apathy and confusion. (v) Muscular twitchings. (vi) Skin pale and moist. (vii) Deep reflexes brisk. (viii) Low blood sugar.

HEAD INJURIES AND THEIR COMPLICATIONS

1. *Brain trauma* – (i) History or evidence of head injury. (ii) Bleeding from nose, mouth or ears. (iii) Respiration rapid, irregular or Cheyne Stokes. (iv) Pulse rapid, later slow. (v) Pupils inactive, often unequal. (vi) Paralysis of cranial nerves. (vii) CSF – blood, with normal pressure.
2. *Chronic subdural haematoma* – (i) History of head injury followed weeks or months later by (ii) headache, nausea, vomiting and disturbances of vision. (iii) Headache of gradually increasing intensity. (iv) Mental symptoms. (v) Weakness in extremities on one or both sides. (vi) Periods of unconsciousness. (vii) CSF – pressure increased, yellowish. (viii) CT scan of skull confirms diagnosis.

Drugs and Poisons

Depression of brainstem reflexes particularly reflex eye movements. Symmetrical signs (see Chapter 15).

INTRACRANIAL INFECTIONS AND TUMOURS

1. *Meningitis* – (i) Gradual onset. (ii) Signs of meningeal irritation. (iii) Fever. (iv) CSF changes.
2. *Brain tumour* – (i) Headache and vomiting. (ii) Visual disturbances. (iii) Neurological signs according to site of tumour. (iv) Progressive course. (v) Papilloedema.
3. *Cerebral abscess* – (i) Course usually more rapid than intracranial tumour. (ii) Evidence of infection like sinusitis, otitis media, lung abscess, etc. (iii) Fever. (iv) Leucocytosis. (v) CSF – increased cells.
4. *Cerebral malaria* – (i) History of fever with rigors. (ii) Spleen may be enlarged. (iii) Fever common; may be hyperpyrexia.
5. *Encephalitis* – (i) Acute onset seizures. (ii) Headache. (iii) Insomnia or drowsiness. (iv) Pupillary and ocular changes. (v) Involuntary movements. (vi) CSF – Normal sugar suggestive. (vii) EEG – Focal abnormalities, PNED.

POST-EPILEPTIC COMA

Diagnostic features – (a) History of GTC seizures. (b) Scars on head from previous falls. (c) Tongue may be bitten. (d) Respiration slow. (e) Pupils fixed during convulsion. (f) Evidence of involuntary defecation or micturition. (g) Recovery usually within an hour without paralytic sequelae, but status epilepticus may be followed by prolonged coma.

COMA OF ENDOCRINE ORIGIN

1. *Hypopituitarism* – Sudden onset if precipitated by infection. Usually female with changes of hypopituitarism. Low BP and low blood sugar.
2. *Myxoedema* – Characteristic appearance with slow pulse and subnormal temperature.
3. *Suprarenal cortical failure* – May occur suddenly as a result of stress, e.g. operation in a patient known to be suffering from cortical deficiency. Low BP and electrolyte disturbances.

PHYSICAL AGENTS

1. *Heat hyperpyrexia and Sun stroke* – (i) Prolonged exposure to high temperature or to heat of sun. (ii) Suffused conjunctivae with contracted pupils. (iii) Hyperpyrexia. (iv) Absence of sweating and dry skin. (v) Circulatory collapse. (vi) Convulsions.
2. *Electric shock* – (i) History of being exposed to electric current. (ii) Evidence of skin burns.
3. *Severe fevers* – e.g. typhoid, typhus – (i) Insidious onset. (ii) Fever of a few days or weeks duration. (iii) Other features or typhoid state.

Psychogenic: *Suggested by* – (i) History of psychological disturbance like hysteria, depressive state or schizophrenia. (ii) Usually occurs in presence of audience. (iii) Not true unconsciousness but severe state of stupor. (iv) Unusual attitudes. (v) Absence of physical signs. (vi) Fluttering of eyelids, resistance to opening and rolling upward of eyeballs. (vii) Normal pupillary reactions. (viii) Normal EEG.

Management of coma: ABC – Airway, Breathing, Circulation to be secured foremost.

1. *Removal or control of cause* – e.g. – Gastric lavage and diuretics in narcotic poisoning; removal of patient to uncontaminated atmosphere and inhalation of oxygen and 5% carbon dioxide in carbon monoxide poisoning; ice bath or covering the patient with ice water sheets and placing under a fan in heat stroke.
2. *Ensure proper respiration* – (i) Keep tongue forward. (ii) Oxygen inhalation. (iii) When there is deep coma, secretions and vomit if inhaled into the lungs, will soon result in death. The patient must be nursed in the semi-prone or lateral position with frequent changes from one side to the other.
3. *Ensure proper circulation* – (a) Parenteral fluids – Glucose saline, plasma, or blood transfusion. (b) Vasopressor drugs like dopamine if low blood pressure or shock.
4. *Care of bowels and bladder* – (i) Indwelling catheter. (ii) Saline or soap enema.
5. *Care of skin* – (i) Frequent change of position in bed. (ii) Alcohol or spirit rub and powdering of skin. (iii) Care of mouth.
6. *Control of secondary infection* – with antibiotics especially in presence of fever or in afebrile patients with the object of preventing pneumonia.
7. *Specific measures* – e.g. for benzodiazepines or organophosphorus poisoning, meningitis, diabetic coma, etc.
8. *Neurosurgical intervention* – if coma progression raises the possibility of herniation.

PSEUDO-COMA STATES

Locked-in syndrome – Damage to the ventral portion of the pons, below the level of IIIrd nerve nuclei, results in locked-in syndrome in which there is total paralysis of the limbs and lower cranial nerves, but consciousness is intact. Patients can open, elevate and depress their eyes but cannot move them horizontally and have no other voluntary movement or speech. The most common cause is infarction of the ventral pons, usually in hypertensive individuals. Locked - in syndrome is also seen in patients with pontine tumors or multiple sclerosis, in central pontine myelinolysis following profound hyponatremia after head injury and after snake bite. EEG is normal.

Classification

- Classic quadriplegia and anarthria with preserved consciousness and vertical eye movements.
- Incomplete: Same as classic but with remnants of voluntary movement other than vertical eye movements.
- Total: Total inability to communicate with full consciousness.

Psychogenic unresponsiveness – The term 'pseudocoma' is used in patients who appear to be unconscious and in coma, but are not. The simplest means of identifying pseudocoma is oculovestibular testing which reveals nystagmus and indicates that the patient has an intact brainstem and cortex (minimally conscious state).

Vegetative state – In the vegetative state, patient breathes spontaneously, and shows cycles of eye opening and closing, but is unaware of the self and the environment. A vegetative state may be seen transiently in recovery from coma, but it may persist to death. It is usually seen in patients with diffuse bilateral cerebral hemisphere disturbance, most commonly after head injury or as a result of hypoxic-ischemic damage following cardiac arrest. Sleep wave cycle is preserved. Some cortical functions may be preserved.

Akinetic mutism – Such patients appear awake but are mute and either fail to respond to stimuli or respond only after very long delays. It is usually caused by severe bifrontal lobe disease. Patients with akinetic mutism have flaccid tone unlike patients in the vegetative state.

BRAINSTEM DEATH

Preconditions for Diagnosis

1. Patient's condition is due to irremediable brain damage of known aetiology.

Table 47: Criteria for diagnosis of brain death

Patient should be examined to ensure that all brainstem reflexes are absent:
• Pupils are fixed in diameter and do not respond to sharp changes in the intensity of instant light.
• No corneal reflex.
• Oculovestibular reflexes absent.
• No motor responses within cranial nerve distribution can be elicited by adequate stimulation of any somatic area.
• No gag reflex or reflex response to bronchial stimulation by a suction catheter passed down the trachea.
• Apnoea confirmed by a $PaCO_2$ > 6.65 kPa measured via arterial blood gas analysis, taken 10 min. after disconnection from mechanical ventilation.
• EEG – Flat (< 2 mV amplitude).
• Absent blood flow on angio.

2. Patient should be deeply comatose, and the effects of depressant drugs, primary hypothermia or potentially reversible metabolic and endocrine disturbances as the cause of continuation of coma must be excluded.
3. Patient is being maintained on a ventilator because spontaneous respiration has become inadequate or ceased.
4. BP is maintained on ionotropes.

Table 47 gives the criteria for diagnosis of brain death.

14. NEUROSYPHILIS

Table 48 gives neurological involvement in syphilis.

Table 48: Clinical manifestations

1. Primary – CSF lymphocytosis.
2. Secondary – Acute syphilitic meningitis.
3. Tertiary:
a. *Meningovascular* – (i) Cerebral or spinal endarteritis. (ii) Cerebral or spinal leptomeningitis. (iii) Meningomyelitis.
b. *Parenchymatous* – (i) General paresis. (ii) Tabes dorsalis. (iii) Primary optic atrophy.
4. Congenital.

ASYMPTOMATIC NEUROSYPHILIS

Diagnosis – If syphilis is untreated for 2 years after primary infection, CNS invasion by Treponema may occur. There are no clinical symptoms or signs. CSF shows increased cells and gives positive VDRL, FTA and TPHA tests. CSF becomes normal 6 months after adequate treatment.

Antisyphilitic therapy prevents development of symptomatic neurosyphilis in future.

MENINGOVASCULAR NEUROSYPHILIS

Cerebral

1. **Cerebral vascular** – Characterized pathologically by endarteritis with thrombosis and encephalomalacia and clinically by various focal neurological signs such as hemiplegia and aphasia.
2. **Cerebral meningeal** –

(a) **Diffuse cerebral meningeal neurosyphilis**

Acute syphilitic meningitis – (i) Acute onset. (ii) Symptoms of increased intracranial pressure – headache, nausea and vomiting. (iii) Evidence of meningeal irritation but Kernig's sign not usually pronounced. (iv) Cranial nerve palsies. (v) Fever. (vi) CSF – 1,000 to 1,500 cells. Thirty percent or more polynuclears; positive for treponemal antibodies (VDRL and FTA - ABS).

*Chronic cerebral leptomening*itis – (a) Basal meningitis – Cranial nerve involvement including optic nerves and chiasma. Hydrocephalus, hypothalamic disturbance may occur. (b) Convexity meningitis – results in headache, drowsiness and focal cortical symptoms including fits.

(b) **Focal cerebral meningeal neurosyphilis** (Gumma) – Signs of expanding intracranial lesion in patient with abnormalities in CSF characteristic of syphilis.

3. **Syphilitic primary optic atrophy** – due to localized syphilitic meningitis. Types – (a) Progressive diminution of vision concentrically from periphery to centre. (b) Wedge-shaped projection. (c) Central visual loss with peripheral vision intact. This is uncommon and does not respond to anti-syphilitic therapy.
4. **Syphilitic dementia or pseudo-general paralysis** – Symptoms closely resembling GPI but cranial nerve paralysis and other indications of widespread lesion.

Spinal

1. *Chronic meningomyelitis* – Initial symptoms due to meningitis – pain in the back, pain in root areas and paraesthesias. Later symptoms due to extension to cord.
2. *Acute transverse myelitis* (Spinal vascular syphilis) – Spinal arterial thrombosis produces myelitis of sudden onset or with premonitory pains, if coexisting syphilitic meningeal involvement. Symptoms of complete or almost complete transection of the cord.

3. *Cervical hypertrophic pachymeningitis* – (i) Pain in neck, radiating down the upper limbs and between the shoulders. (ii) Progressive weakness and atrophy of muscles supplied by the corresponding anterior roots. (iii) Finally progressive spastic paraplegia with sensory loss below level of lesion. CSF – Mild or moderate lymphocytic pleocytosis, protein content greatly elevated.
4. *Erb's spastic paraparesis* – Progression of paraparesis is very slow and there is little sensory loss.
5. *Spinal gumma* – Symptoms of rapidly growing spinal tumour.
6. *Syphilitic amyotrophy* – Closely resembles idiopathic progressive muscular atrophy or amyotrophic lateral sclerosis. Sensory loss absent or minimal. Pain in the affected limb may occur at onset and is sometimes severe. Treponemal tests positive. Anti-syphilitic treatment arrests progress of the disease.
7. *Radiculitis* – Syphilis usually affects the posterior roots which gives rise to pain of segmental distribution. If anterior roots are affected, there is weakness and wasting of the segmental muscles.
8. *Pseudotabes* – Onset 18 months to 5 years after primary infection. Presents with root pains, absent deep reflexes and bladder disturbances. No AR pupils.

PARENCHYMATOUS NEUROSYPHILIS

General Paresis of the Insane (GPI)

Clinical Features: Stages

1. *Incipient stage* – Presenting symptoms often vague as in dementing illness, ill-defined personality changes with irritability and forgetfulness, poor concentration, headaches and weight loss.
2. *Period of full development of psychosis* – Multiform psychic pictures – (a) Simple demented type – Memory defect, impairment of judgement and lability of mood going on to imbecility. (b) Grandiose type – Sense of euphoria and expressions of delusions of grandeur.
3. *Terminal stage or period of decline* – Fits, sometimes with transient neurological deficits may accompany deterioration or occasionally herald it. Motor signs gradually appear.

Signs – (i) Pupillary abnormalities often of Argyll-Robertson type. (ii) Cranial nerves –Optic atrophy much less common than in tabes. Coarse tremors of facial, labial and tongue muscles. (iii) Slurred and tremulous speech, micrographia and inability to write in straight line. (iv) Exaggerated deep reflexes, plantars extensor. (v) Tabes dorsalis may co-exist (Taboparesis).

CSF – Moderate pleocytosis, 15–100 cells per cmm., increased protein and positive antibody tests.

Tabes Dorsalis

Basic lesion is in the root entry zone of the posterior nerve roots and there is ascending degeneration of the posterior columns, diagnostic features are referable to these.

Clinical Features

1. *Subjective sensory disturbances* – (a) Pains – (i) typical lightning pains; (ii) fixed pains; (iii) girdle pains; (iv) pains of tabetic crisis. (b) Feeling of walking on cotton wool.
2. *Objective sensory loss* – Butterfly area on face, inner side of arms, saddle-shaped area round anus, feet. Anaesthesia of tendo Achilles (Abadie's sign).
3. *Hypotonia* – Abnormal active and passive movements of the limbs; "double jointed" man.
4. *Ataxia.*
5. *Reflexes* – Early loss of ankle jerks; plantars always flexor unless complicated by GPI (Taboparesis).
6. *Ocular signs* – Pupils usually contracted and irregular or unequal in size, sluggish reaction to light. AR pupil in late stages. Optic atrophy may be early; ptosis, transient paralysis of external ocular muscles, diplopia.
7. *Sphincters* – Difficulty in micturition or incontinence or sometimes retention. Faecal incontinence may occur. Impotence sometimes an early symptom.
8. *Trophic changes* – (a) Perforating ulcer usually of pad of great toe. (b) Charcot's joints.
9. *Gait* – (a) Wide-based, (b) eyes fixed to the ground, (c) legs lifted unduly in air, and (d) brought down with a stamp.
10. *Crisis* – Paroxysmal painful disorders of function of various viscera – Gastric crises, the commonest may cause epigastric or, shoulder tip pain with or without vomiting or vomiting without pain.

CSF – Cells usually not above 100/cmm., mononuclear cells, excess of globulin.

CONGENITAL NEUROSYPHILIS

Clinical features – and course similar to those seen after infection in later life. (a) Meningovascular disease is seen during first few years after birth. (b) GPI may occur during school years and present as simple deterioration in performance with fits. (c) Tabes is much less common. (d) Isolated perceptive deafness may present in middle age.

LABORATORY DIAGNOSIS OF NEUROSYPHILIS

Blood serology – In active neurosyphilis VDRL positive in about 75% and TPHA test and FTA-ABS test in nearly all cases. If blood tests are positive, disease activity should be further assessed by CSF examination.

CSF – (a) *Serology* – Positive VDRL is more likely to indicate active disease than positive specific serology. (b) *Cell count and proteins* – Active neurosyphilis of any variety produces increase in mononuclear cells to about 200/mm^3, mainly lymphocytes and rise in protein to about 2 g/litre. (c) *IgG* – Electrophoresis often shows elevation of cathodal IgG which may be diffuse or banded.

TREATMENT: OF NEUROSYPHILIS

1. *Prednisolone* – 40 mg daily for 3 days to prevent Herxheimer reaction (most likely to occur in GPI or when CSF cell count is raised). A longer course in optic atrophy may be helpful.
2. *Specific therapy* – Aqueous crystalline penicillin G (18–24 mU/d IV given as 3–4 mU q4h or continuous infusion) for 10–14 days or Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days. In case of patients allergic to Penicillin, desensitization and treatment with penicillin.

   Follow-up – CSF cell count should return to normal within 3 months, protein within 6 months. This response should be checked by repeat lumbar puncture at 6 weeks and 3 months after completion of therapy and thereafter at 6 monthly intervals until cells and proteins have been normal on two consecutive occasions. The IgG, and serology often revert but may remain abnormal for long periods.
3. *Symptomatic treatment* – may be required for confusion, ataxia, urinary retention and Charcot's joints.

15. TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

CLINICAL MANIFESTATIONS

1. **Tuberculous meningitis**
2. **Intracranial tuberculoma** –

   Clinical features – (a) Age – Any but more common below 10 years. (b) Site – In paediatric age group it is common in posterior fossa, while in adults it is common supratentorially. (c) Symptoms and signs – (i) Due to raised intracranial pressure – Headache, vomiting, papilloedema. (ii) Focal abnormality depending on site of lesion (hemiparesis, ataxia).

   Investigations – (a) For site of lesion – CT scan, angiography, MRI (Figs. 35 to 37). (b) For evidence of tuberculous diathesis – ESR, X-ray chest, tuberculin test. CT chest and abdomen.

   Management – Antituberculous therapy, measures to relieve intracranial tension, and surgical excision of tumour mass. AKT for 1–2 years.
3. **Pott's paraplegia** –

   Pathogenesis – Incidence of spinal tuberculosis is more than 50% of all bone and joint tuberculosis. It can occur at any age and sex incidence is equal. Spinal

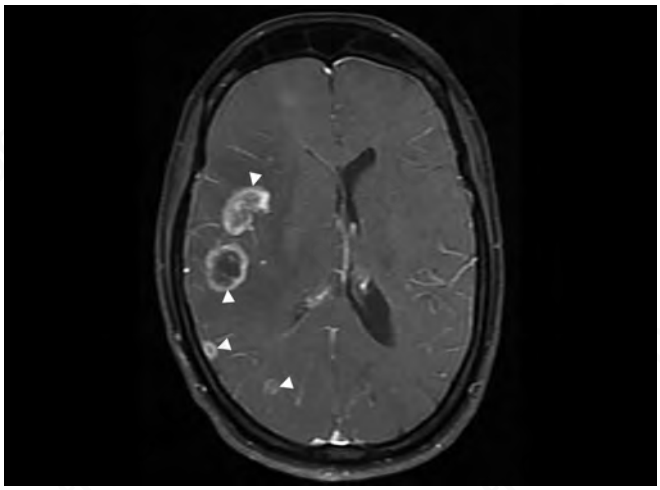


Fig. 35: MR post-contrast showing multiple tuberculomas (arrowheads)

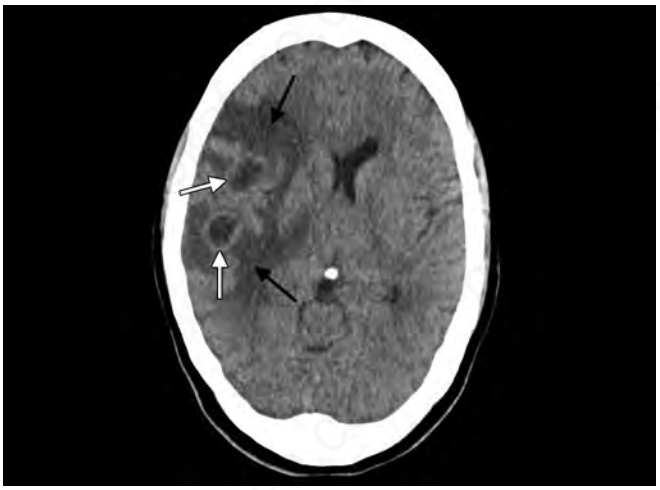


Fig. 36: CECT showing multiple tuberculomas (white arrows) with surrounding oedema (black arrows)

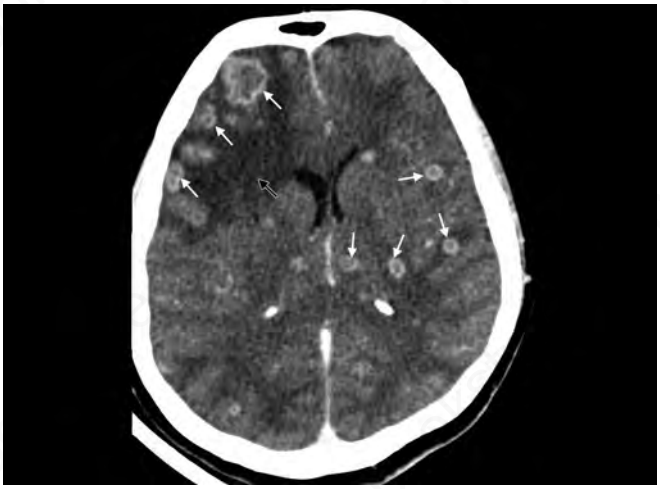


Fig. 37: CECT showing multiple tuberculomas (white arrows) with surrounding oedema (black arrow)

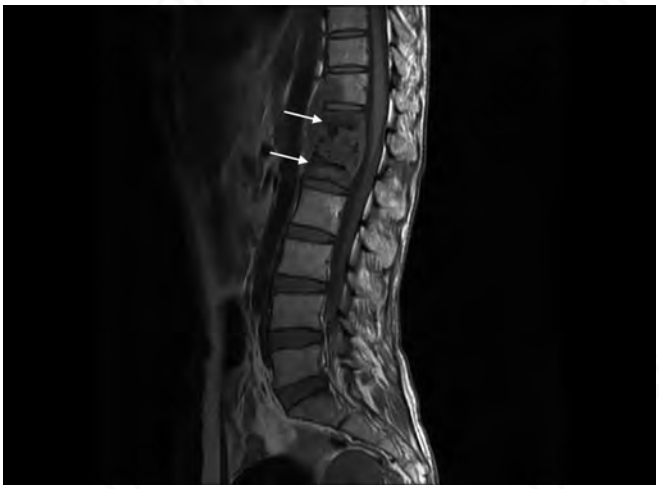


Fig. 38: Potts spine involving D12 and L1 vertebrae (arrows)

cord compression may be due to – (a) Fluid abscess in spinal canal. (b) Paraspinal abscess invading spinal canal. (c) Granulomatous tissue invading spinal canal. (d) Dislocated vertebra. (e) Thick transverse ridge of granulomatous tissue producing compression. (f) Spinal phlebitis resulting in venous infarction of the spinal cord and syringomyelia (secondary).

Clinical features – Subacute or chronic onset of paraparesis or paraplegia, symmetrical or asymmetrical, preceded or followed by root pains and paraesthesiae. Level of objective sensory loss. Sphincter involvement usually late. Spinal deformity (gibbus) and spinal tenderness.

Investigations – (a) For confirmation of diagnosis of extramedullary compression – X-ray spine, MRI, CT (Fig. 38). (b) For confirming aetiology – ESR, X-ray chest, histopathology of lesion.

Management – Immobilization, antituberculous chemotherapy with steroids. Laminectomy and removal of granulomatous mass or aspiration of abscess.

4. **Arachnoiditis** – Chronic spinal meningitides due to inflammation of all three layers of spinal theca. May be of primary spinal variety, or secondary to vertebral tuberculosis or tuberculous basal meningitis.

Clinical features – (a) Subacute form – Maximal severity is reached within 2–5 days. Symptoms of root pains, paraesthesiae, paralysis, bladder disturbance, and wasting of muscles. General symptoms of low grade fever, malaise and anorexia. The disease may present as a single-level lesion resembling spinal tumour, or multifocal radiculopathy and/or myelopathy with or without vasculopathy, or an ascending variety with affection of lumbosacral roots

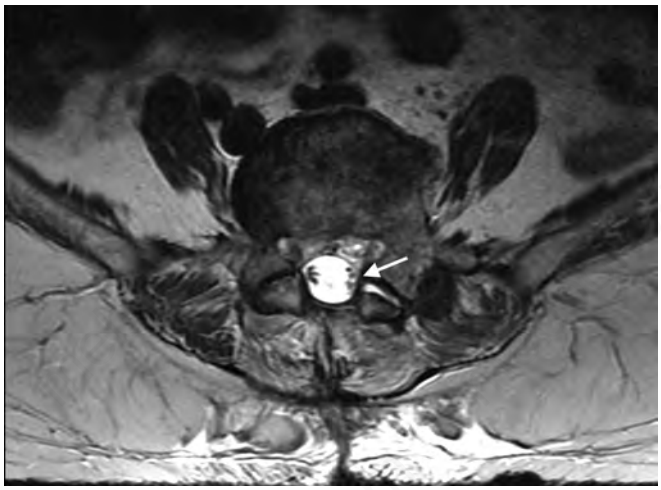


Fig. 39: Arachnoiditis seen on MRI axial T2 image (arrow)

and severe sciatica followed by an areflexic hypotonic limb and bladder paralysis, and sensory loss. Soon the sensory loss, root pains and paralysis ascend to involve all four limbs (b) Chronic form – May progress slowly over months or years simulating a spinal tumour with lesion localised to a single level, or with multifocal spinal cord lesions.

Investigations – (a) *Plain X-ray of spine* – may show vertebral caries. (b) *CSF* – Typically there is lymphocytic proliferation with 50-100 cells/cmm, and marked rise in proteins even up to 2–3 gm/100 mL. (c) *MRI* – Meningeal enhancement, thickening and clumping of nerve roots (Fig. 39).

Management – Antituberculous therapy, high doses of steroids with intrathecal steroid administration, and physiotherapy.

Table 49: Classification of intracranial tumours

1. **Tumors of neuro-epithelial origin**	
• Astrocytic tumours	Astrocytoma (most common primary benign tumour)
	Glioblastoma (Fig. 40)
	Pilocytic astrocytoma
• Oligodendroglioma	
• Ependymoma	
• Choroid plexus papilloma/carcinoma (Fig. 41)	
• Pineal cell tumours	
• Ganglioglioma	
• Neuroblastoma/neurocytoma	
• Medulloblastoma (uncommon in adults) (Figs. 42 and 43) Primitive neuro-ectodermal tumours	
Tumours of nerve sheath origin	
• Schwannoma (Fig. 44)	
• Neurofibroma	
Meningeal tumours	
• Meningioma	
• Meningeal sarcoma	
Tumours of mesenchymal origin Haemangiopericytoma	
Primary cerebral lymphoma	
Tumours of uncertain histogenesis	
• Haemangioblastoma	
Tumours of germ cell origin	
• Germinoma	
• Teratoma	
Pituitary tumours	
• Pituitary adenoma	
Others	
• Craniopharyngioma	
• Colloid cyst (Fig. 45)	
• Dermoid cyst	
• Epidermoid cyst	
Cerebral metastasis (Fig. 46)	
Local extension from head and neck tumors	
• Chordoma	
• Glomus jugulare tumour	
Infective granulomas	
• Tuberculoma	
• Gumma	
Parasitic cysts	
• Cysticercus	
• Echinococcus	

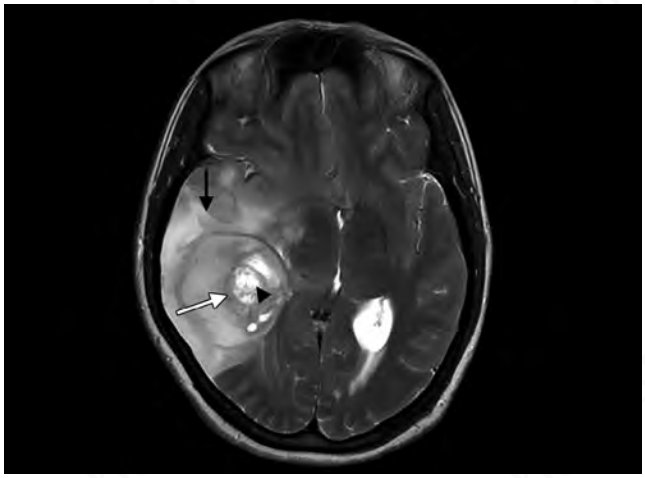


Fig. 40: MRI T2 image showing glioblastoma multiforme (white arrow) with hemorrhage inside (black arrow head) and surrounding oedema (black arrow)

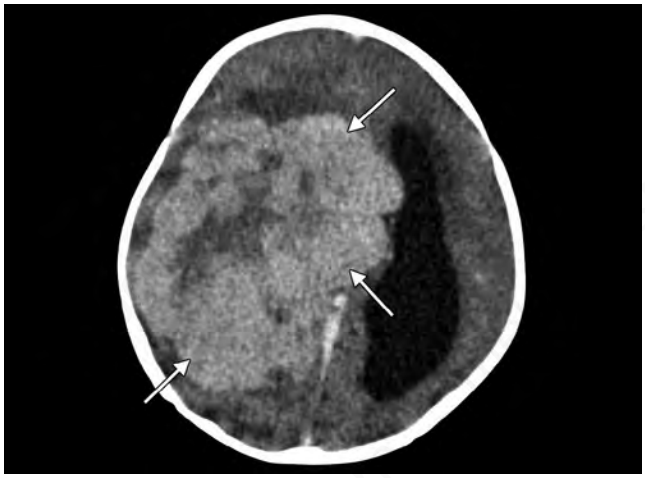


Fig. 41: CECT showing choroid plexus papilloma (arrows)

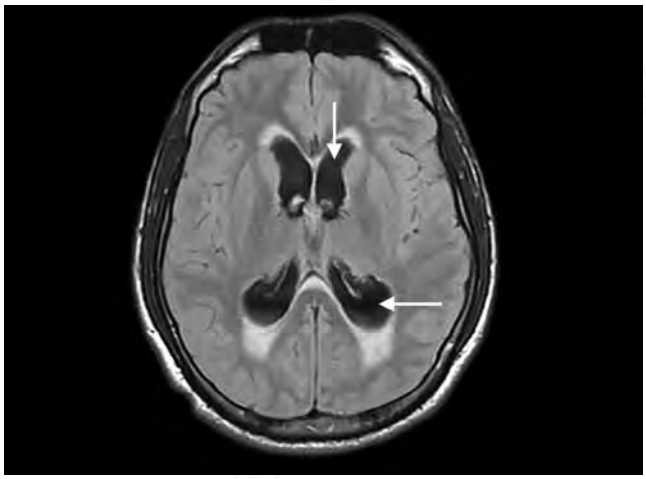


Fig. 42: MRI axial Flair image showing decompensated hydrocephalus due to medulloblastoma with periventricular ooze

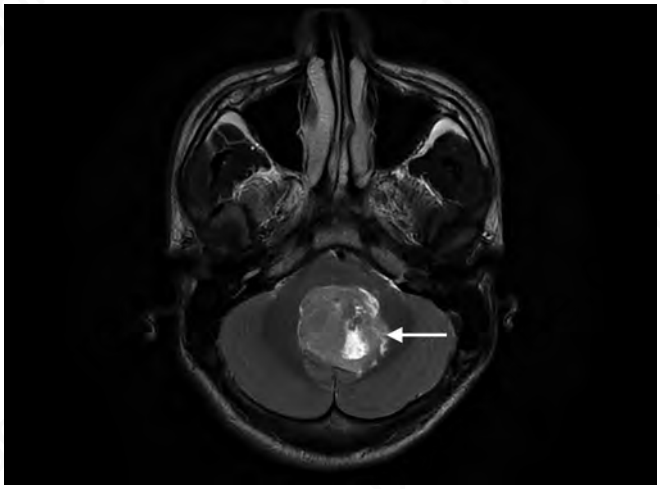


Fig. 43: MRI axial T2 image showing medulloblastoma (arrow) in patient in Figure 42

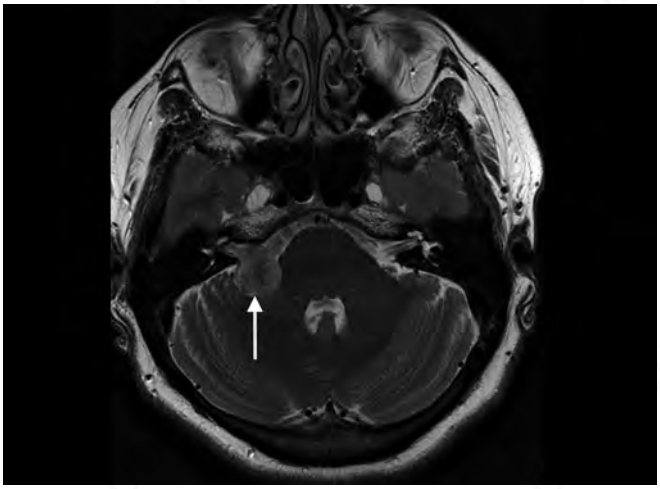


Fig. 44: MRI axial T2 image showing right VIIth VIIIth nerve complex schwannoma (arrow)

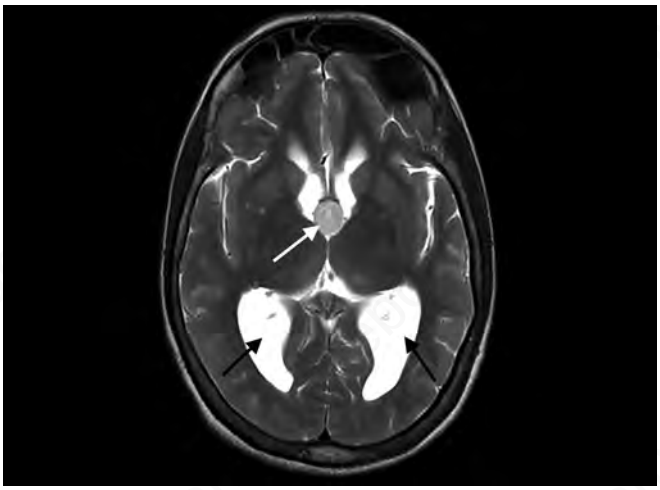


Fig. 45: MRI axial T2 image showing hydrocephalus (black arrow) due to colloid cyst (white arrow) in third ventricle

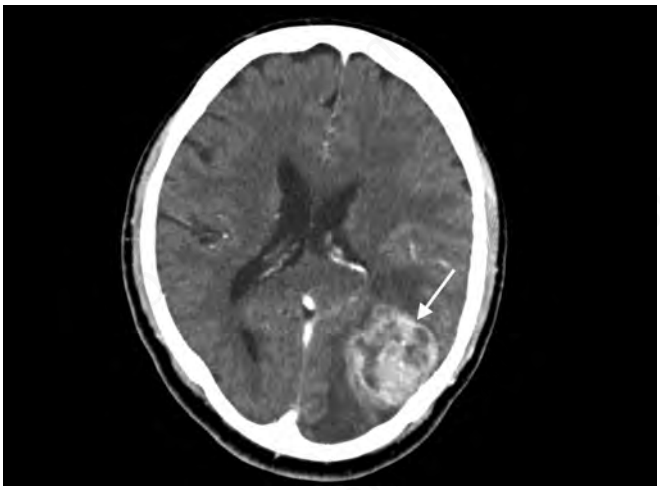


Fig. 46: Brain metastasis from melanoma

16. INTRACRANIAL TUMOURS

Table 49 gives classification of intracranial tumours.

CLINICAL FEATURES

Symptoms

1. *Raised intracranial pressure* may be the result of – (a) the mass itself. (b) Associated cerebral oedema. (c) Obstruction of CSF pathways causing hydrocephalus as in many tumors of posterior fossa:
   (a) *Headache* – tends to occur in early morning and is usually described as vice-like or gripping pain, aggravated by activities which increase intracranial pressure such as coughing and straining. (b) *Vomiting* – is sudden, projectile and not preceded by nausea. (c) *Visual disturbance* – Progressive loss of visual activity usually with episodes of transient blindness in both eyes (visual obscurations) lasting only a few seconds but increasing in duration and frequency with increasing intracranial pressure. (d) *Altered consciousness level* – in the form of acute and profound deterioration, or increasing lethargy and 'general slowing down' of the patient noticed by the family. (e) *Intellectual deterioration*, incontinence and disequilibrium, if pressure increases over long period. (f) *Drowsiness followed by coma,* if rapidly rising intracranial pressure.

2. *Epilepsy* – is the presenting feature in up to 50% of tumours.
3. *Focal neurological deficits* – depend on the location of the tumour. Gradual onset of hemiparesis, hemianopia or dysphasia is typical of many supratentorial gliomas. Frontal lobe tumors typically cause a loss of affect with self-neglect and intellectual deterioration. Tumors in posterior fossa give rise to ataxia, dysarthria and brainstem and cranial nerve signs.

   Associated features – may include:
   - Signs of systemic malignancy.
   - Focal effects from tumours at base of skull, e.g. proptosis, epistaxis.
   - Features of a neurocutaneous syndrome associated with tumours, e.g. neurofibromatosis.
   - Endocrine or developmental disturbance.

INVESTIGATIONS

1. ***CT*** – is more specific and sensitive with respect to diagnosis and location (Figs. 47 and 48) than radiography and isotope scans.
2. ***MRI*** – however provides better images of lesions in the posterior fossa, around the skull base and suprasellar regions, and in the pineal region. MRI is more sensitive in detecting low-grade gliomas and demonstrating multiple metastases. When a tumour is identified in a child, the whole spine should be imaged to look for 'drop' metastases along the neuraxis.
3. ***Plain radiography of skull*** – (in absence of CT or MRI): (a) Features of raised intracranial pressure – In adults erosion of pituitary fossa, especially the lamina dura and occasionally "copper beating" or "beaten brass" appearance of skull. In children skull sutures may be separated up to 10 years of age. (b) Displacement of calcified pineal gland by a large lesion in one hemisphere. (c) Calcification of the lesion: Astrocytoma, oligodendroglioma and craniopharyngioma. (d) Hyperostosis of overlying skull: meningioma. (e) Erosion of normal structures, e.g. acoustic neuroma widening the external auditory meatus.
4. ***Chest radiograph*** – to exclude primary tumours of bronchus and to help to detect secondary tumours from other sources.
5. ***Cerebral angiography*** – Tumours of the brain are localized by displacement of arteries and veins and by presence of abnormal vascular patterns. Of particular value in differential diagnosis of brain tumour from cerebral vascular lesions, aneurysm and angiomatous malformations.
6. ***EEG*** – is not a primary aid, but abnormalities consistent with hemisphere or deep central lesions, or with hydrocephalus, may be recognised.

DIFFERENTIAL DIAGNOSIS

Other Conditions Causing Increased Intracranial Pressure

I. Infection:

1. ***Intracranial abscess*** – Source of infection – (a) Haematogenous – SIE, congenital heart disease (e.g. right to left shunt), bronchiectasis or lung abscess. (b) Intracranial spread – Compound depressed fracture of skull, frontal sinusitis, chronic otitis media, mastoiditis, extension of infected thrombus.

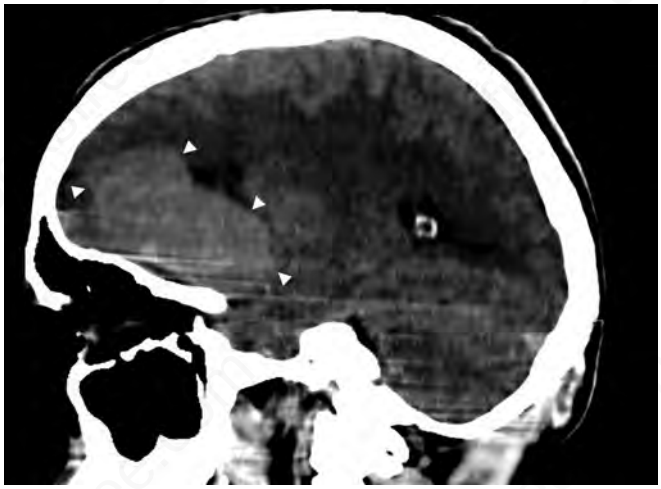


Fig. 47: CT showing hyperdense meningioma of sphenoid ridge (arrowheads)

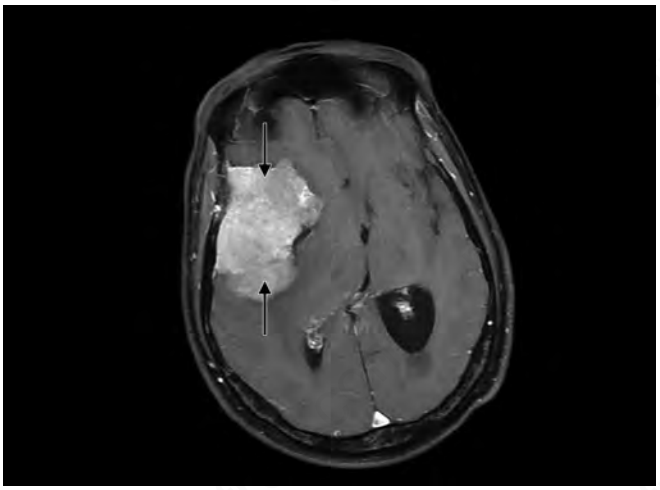


Fig. 48: Meningioma showing postcontrast enhancement (arrow)

Clinical features – (a) Of toxaemia – Pyrexia, malaise. (b) Raised intracranial pressure – Headache, vomiting. (c) Focal damage – Hemiparesis, dysphasia, ataxia. At times seizures. (d) Infected site – Ear discharge, cardiac murmurs.

Investigations – (a) X-ray of sinuses and mastoid. (b) CT scan with IV contrast – Midline shift from mass effect, ring enhancement, central area of low density, and surrounding area of low density due to oedema.

2. ***Tuberculoma*** – Clinical features of intracranial mass. Skull X-ray – may show calcified tuberculoma (Fig. 49). CT scan – Lesion resembles astrocytoma or metastasis. Reduction in lesion after antituberculous therapy.
3. ***Neurosyphilis*** – (a) Meningovascular – Cranial nerve palsies, pupillary changes, positive serology and characteristic CSF changes. (b) Cerebral gumma – very rare; response to antisyphilitic therapy.

II. Vascular

1. ***Cerebral infarct*** – Hemiparesis, hemisensory loss and dysarthria. Hemianopia may occur. A large infarct impairs consciousness. CT scan shows the infarct.
2. ***Cerebral venous and/or dural sinus thrombosis*** – Secondary to intracranial suppurative disease or presence of generalised hypercoaguable state, e.g. cyanotic heart disease, pregnancy and puerperium, dehydration. Slow evolution of symptoms resembling encephalitis, or sudden onset with focal seizures. CT scan appearance of haemorrhagic infarction.

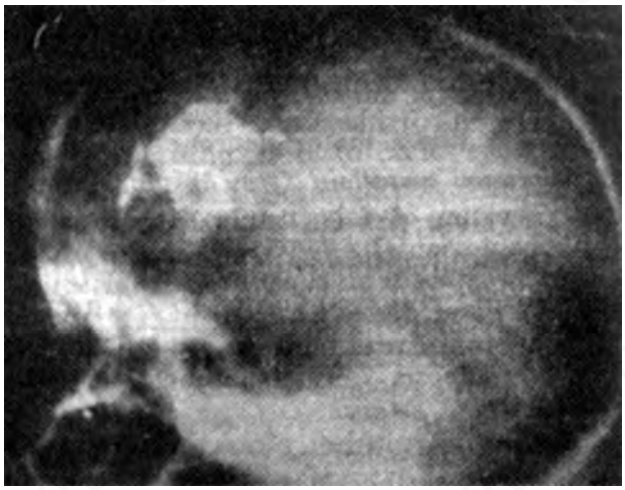


Fig. 49: Intracranial calcification due to tuberculoma

3. ***Intracranial aneurysm*** – (a) Before rupture – Symptoms due to pressure on surrounding structures but very slowly progressive, headache slight, no papilloedema. Angiography to confirm diagnosis. (b) After rupture – Headache, secondary optic atrophy and sometimes focal cerebral symptoms. History of acute episode.
4. ***Subdural haematoma*** – Symptoms and signs fall into 3 groups:
   (a) *Due to raised ICP* – Headache, nausea, vomiting, dizziness, convulsions.
   (b) *Due to fluctuation in volume of contents of haematoma* – State of consciousness varies from lapse of memory to aberrations of behaviour or coma. Semicomatose or mental stupor may develop in a few days or few hours.
   (c) *Due to local pressure on adjacent structures* – Diplopia, ocular palsy, hemiparesis and generalized fits may occur.

   Diagnosis – confirmed by CT scan.
5. ***Malignant hypertension*** – Severe headache and papilloedema with perhaps a focal cerebral lesion. B.P. high, haemorrhages and cotton wool patches in retina; enlargement of heart, progressive, and evidence of renal insufficiency.
6. ***A-V malformation*** – (a) Seizures generalized or partial especially, if involvement of cerebral cortex. (b) Neurological deficit – if large malformation – Slowly progressive – dementia, hemiparesis or visual field defects. (c) Headache – Well localized, unilateral, throbbing. (d) Bruit may be heard over eyeball. CT scan – AVM easily seen as area of mixed density with high density patches (calcification). After IV contrast dilated vessels seen as streaks of enhancement. Four vessel angiography confirms presence of AVM and delineates the vessels.

III. Hydrocephalus

(a) *Congenital* – Enlargement of head, slowly progressive wide anterior fontanelle, dilatation of scalp veins. 'Cracked pot' sound on skull percussion 'Setting sun' appearance of eyes, vomiting rare, mental deficiency.

(b) *Acquired* – (i) Raised intracranial pressure. Headaches often worse in morning. Nausea and vomiting. Occasionally blurred vision. Eventually drowsiness leading to depressed consciousness level – papilloedema conspicuous, with little headache

and vomiting. No focal signs. (ii) Due to meningitis – History of meningitis. Headache at first paroxysmal, later constant with intense exacerbations; cranial nerve palsies common. CT scan shows enormous dilatation of the ventricular system.

IV. *Benign intracranial hypertension (Pseudotumour cerebri)*

Condition of raised intracranial pressure not due to expanding mass lesion or obstruction to CSF flow. Mechanism unknown. *Possible causes* – (i) Diet – obesity, hyper/hypovitaminosis A. (ii) Endocrine – Hypoparathyroidism, Cushing's syndrome, Addison's disease, menopause. (iii) Haematological – Iron deficiency anemia, polycythemia vera. (iv) Drugs – Oral contraceptives, nalidixic acid, tetracycline, steroid administration or withdrawal. (v) Chronic respiratory insufficiency. *Clinical features* – Age – Predominantly between 10–15 years. Headache, vomiting, impaired visual acuity from papilloedema, diplopia from VI nerve palsy. *Investigations* – (i) Visual field charting – enlarged blind spot, peripheral field constriction. (b) Lumbar puncture – and pressure measurement. CT scan – Small ventricles, no mass lesion.

V. *Increased intracranial pressure (ICP)*

May be due to (a) intracranial causes, e.g. cerebral tumour, subdural hematoma, intracerebral hemorrhage, obstructive hydrocephalus, benign intracranial hypertension. Major sinus vein occlusion, post neurosurgery. (b) Extracranial cause - Hypoventilation, convulsions, hyperpyrexia, drug induced (e.g. tetracycline, valproate), hepatic failure, high altitude, cerebral oedema. Cl. Fs. - If acute rise in ICP - Cushing's triad (bradycardia raised BP, respiratory depression), drowsiness, papilloedema, if ICP persists for more than a few days.

VI. *Cysts*

Arachnoid or hydatid – may present as intracranial mass. CT scan – shows a low density, well-demarcated lesion. In cerebral cysticercosis – Epileptic fits, palpable subcuticular cysts in muscles or subcutaneous tissues, eosinophilia.

Disorders Causing Progressive or Recurrent Symptoms

1. ***Cerebral atheroma*** – Carotid artery stenosis may present as a slowly progressive lesion, symptoms and signs developing over weeks or months. Progressive mental deterioration, hemiplegia and headache simulate cerebral neoplasm. Unilateral or bilateral papilloedema may be present. Carotid bruit often heard. Angiography and other investigations confirm diagnosis.
2. ***Epilepsy*** – Convulsions starting after age of 25 should suggest possibility of tumour. Investigations must be done to determine, if epilepsy is due to tumour (if focal seizure).

Management – Definitive treatment is based on the specific tumor type and includes surgery, radiotherapy and chemotherapy. But patient needs simultaneous symtomatic treatment

For raised intracranial tension: (a) Posture with head elevated. (b) *Mechanical hyperventilation* reduces arterial PaO_2 which in turn reduces blood volume and blood flow. Raised ICP begins to fall 10-30 seconds after hyperventilation, reaches its nadir in 10 mins and returns to its original level in less than an hour. There is thus limited time for effective ICP control with hyperventilation. (c) *Osmotic dehydration* - (i) Mannitol 0.25 g/kg infused rapidly and given 2–3 times/day. (ii) Glycerol 1.5 g/kg body wt/d in 3–4 divided doses diluted with fruit juice to mask the unpleasant taste. Serum osmolality and urine output should be measured frequently. (iii) Frusemide 20–40 mg bd for causing diuresis. BP and electrolytes to be checked. (iv) Acetazolamide 250–500 mg/day helps to restrict CSF formation. (v) 3% hypertonic saline can be used not only in cases of hyponatremia, but also sometimes as an osmotic diuretic. (d) Glucocorticoids are highly effective at reducing perilesional edema and improving neurologic function within hours of administration. Dexamethasone has been the glucocorticoid of choice, doses are typically 12–16 mg/d in divided doses given orally or IV.

Patients who present with seizures require antiepileptic drug therapy. There is no role for prophylactic antiepileptic drugs in patients who have not had a seizure.

HERNIATION SYNDROMES

Transtentorial Syndromes

- Central herniation - Expanding lesions of frontal, partial or occipital lobes or midline extracerebral tumors may produce a downward movement of midline intracranial structures into the posterior fossa. Initial focal features relating to the lobe of origin are soon

replaced by diencephalic symptoms as hernia begins. Wider fluctuations of temperature and impairment of upgaze. Later brainstem symptoms, including respiratory and hemodynamic disturbances appear.

- Uncal herniation produces deterioration of sensorium, ipsilateral dilatation of pupil, contralateral hemiparesis and decerebrate posturing.
- Cerebellar tonsillar herniation through the foramen magnum can occur due to rapidly expanding hemorrhage, infarcts or mass lesion in posterior fossa. Cerebellar symptoms and signs rapidly evolved to medullary dysfunction with coma, decerebrate posturing and respiratory impairment.
- Subfalcine or cingulate herniation may cause occlusion of anterior cerebral artery and its branches with widespread infarction.

17. DISORDERS OF THE SPINAL CORD

PARAPLEGIA

Paraplegia is paralysis confined to the lower limbs. Table 50 gives classification of causes of paraplegia.

Common causes of spastic paraplegia are – (1) Transverse myelitis. (2) Spinal cord compression including tuberculosis of spine. (3) Anterior spinal artery occlusion. (4) Trauma to spine.

Investigation of A Case of Paraplegia

A. Is the difficulty in walking due to other causes?

1. Decreased muscle power.
2. Disturbances of tone, e.g. Parkinsonism.
3. Cerebellar disorder causing ataxia, and chorea.
4. Loss of postural sense, e.g. diabetes, tabes dorsalis.
5. Hysteria.

B. Is the paraplegia hysterical or organic?

Hysterical Paraplegia

1. Plantar response never extensor.
2. No correlation between distribution of sensory loss and known anatomical distribution, or glove and stocking type of anaesthesia. Bilateral anaesthesia rare. Patient does not burn or cut the anaesthetic skin.
3. Motor power may be normal when recumbent, yet patient cannot stand (astasia abasia).
4. Hysterical rigidity – Rigidity shows variation from moment to moment.
5. Reflexes normal or exaggerated.
6. No sphincter disturbances.

Table 50: Classification of causes of paraplegia

I. ***Due to upper motor neuron lesion***

A. **Intracranial causes**

- Tumour of falx cerebri (parasagittal meningioma).
- Thrombosis of superior sagittal sinus.
- Cerebral diplegia.
- Hydrocephalus.
- Thrombosis of unpaired anterior cerebral artery.
- ACA infarcts.

B. **Spinal causes**

Systemic degeneration of tracts

- Subacute combined degeneration
- Multiple sclerosis
- Amyotrophic lateral sclerosis
- Syringomyelia
- Friedreich's ataxia.

Secondary affections of white matter

- *Trauma* – Fracture dislocation, Kummel's disease.
- *Infection* – Acute transverse myelitis, epidural abscess, syphilis.
- *Vascular* – (i) Haemorrhage – (a) Intrathecal (haematomyelia). (b) Intramedullary (spinal epidural haematoma). (ii) Thrombosis (myelomalacia). (iii) Spinal A-V malformations.
- *Compression*
  Acute – Common: Metastatic tumour (Fig. 50). Rare – Infection, spontaneous hematoma, cervical or thoracic disc, intrinsic tumour.
  Chronic – Common: Cervical spondylosis. Rare: Neurofibroma, meningioma, intrinsic tumour, congenital cysts, thoracic disc, syringomyelia, inflammatory disease, arachnoiditis.
- *Chronic malnutrition* – Pellagra.
- *Toxins* – Lathyrism, fluorosis.
- *Radiation myelopathy.*

II. ***Due to lower motor neuron lesion***

- *Anterior horn cell* – Acute anterior poliomyelitis, spinal muscular atrophies, motor neuron disease.
- *Peripheral nerve* – Peripheral neuropathy, Guillain-Barre syndrome.
- *Myoneural junction* – Myasthenia gravis, familial periodic paralysis.
- *Muscles* – Muscular dystrophies, polymyositis.

Table 51: Differences between upper motor and lower motor neuron paralysis

UMN lesion	*LMN lesion*
1. Paresis of movement	1. Paralysis of individual muscles or muscle group
2. Diffuse distribution	2. Distribution confined to individual muscles
3. Spasticity	3. Hypotonia
4. No muscular wasting	4. Muscular atrophy. Fasciculations
5. Brisk reflexes	5. Hypo or areflexia
6. Extensor plantar response	6. Flexor plantar response
7. Associated involuntary movements (flexor spasms)	7. No associated involuntary movements
8. Electrical reaction normal	8. Reaction of degeneration

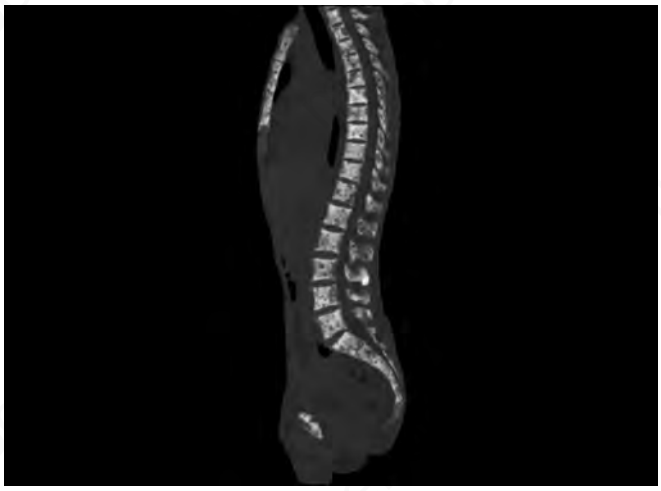


Fig. 50: MRI showing multiple metastases from carcinoma of prostate into the spine

C. Is it upper motor or lower motor neuron paralysis? (Table 51)

D. Is the paraplegia due to localized or system disease of the spinal cord?

In localized disease signs and symptoms are referable to one or two segments of the cord. In system disease symptoms and signs are referable to various systems of the nervous system. (Sensory, motor, cerebellar, extra-pyramidal).

Investigation of a Case of Spastic Paraplegia

I. History

1. Onset
   (a) *Acute* – Spinal: Acute transverse myelitis, trauma (fracture dislocation of spine), prolapsed disc, vascular disorders (infarction or haemorrhage), epidural abscess, hysteria. Cerebral – Superior sagittal sinus thrombosis, thrombosis of unpaired anterior cerebral artery.
   (b) *Subacute* – Developing over two or three days – Acute myelitis, compression of spinal cord, e.g. tuberculous spinal osteitis or pyogenic extradural abscess or rarely secondary carcinoma of spine.
   (c) *Insidious* – Meningomyelitis, subacute combined degeneration, cervical spondylosis, amyotrophic lateral sclerosis, spinal tumour, syringomyelia, multiple sclerosis, cauda equina and conus medullaris lesions and sometimes lathyrism. General paralysis of insane, hereditary spastic paraplegia, and ischemic degeneration of spinal cord due to atherosclerosis.
   (d) *Unilateral* – onset in spinal tumour.
2. Age
   (a) *Children* – Cerebral diplegia, hydrocephalus, meningitis, spina bifida, spinal caries and superior longitudinal sinus thrombosis.
   (b) *Adult* – Common are spinal tumour, TB spine, transverse myelitis, amyotrophic lateral sclerosis, syringomyelia, multiple sclerosis and craniovertebral anomalies.
   (c) *Middle and old* – Cervical spondylosis, subacute combined degeneration, secondary deposits, Paget's disease, progressive cervical myelopathy.
3. Family history – (a) In subacute combined degeneration more than one member of family may have evidence of paraplegia, neuritis or pernicious anaemia. (b) In lathyrism more than one member of family affected, and history of consumption of lathyrus pulse. (c) Familial incidence in hereditary spastic paraplegia.
4. History of trauma – Fracture dislocation of spine or haematomyelia.
5. History of syphilis.

6. Recurrent paraplegia – Multiple sclerosis, periodic paralysis, recurrent spinal ischemia, A-V malformation with minor bleed or oedema, hysterical.
7. Symptoms –
   (a) *Pain* – Constant or intermittent in extramedullary spinal tumour; may be aggravated by coughing or straining. Root pains in radicular spinal syndrome, syringomyelia.
   (b) *Numbness and tingling* – Subacute combined degeneration, spinal tumours, disc protrusion, fluorosis.
   (c) *Progress of symptoms* – Frequent arrests in multiple sclerosis and syringomyelia. Rapid progress in malignant deposits.
   (d) *Psychological symptoms* – Euphoria common in multiple sclerosis. Mental symptoms in subacute combined degeneration and GPI. Mental deficiency in cerebral diplegia.
   (e) *Fever* – may be present with tuberculosis of spine, or epidural abscess.

II. Physical examination

1. Speech – Staccato speech in multiple sclerosis; dysarthria in amyotrophic lateral sclerosis and syringomyelia.
2. Cranial nerves – Optic atrophy (Table 52). Paralysis in intracranial tumours. Nystagmus in multiple sclerosis. Pupillary changes in neurosyphilis. Inability to swallow in amyotrophic lateral sclerosis.
3. Motor system:
   (a) *Wasting* – in presence of increased jerks suggestive of amyotrophic lateral sclerosis. Combination of upper motor paralysis in lower extremities and lower motor in upper extremities:
      - Amyotrophic lateral sclerosis
      - Syringomyelia
      - Hypertrophic cervical pachymeningitis, and
      - Compression of cervical region by tumour or cervical disc degeneration,
   (b) *Co-ordination* – Ataxia combined with spasticity in early stage of subacute combined degeneration; multiple sclerosis, Friedreich's ataxia, cervical spondylotic myelopathy, craniovertebral anomalies.
   (c) *Involuntary movements* – Tremors in multiple sclerosis. Muscular fasciculations in amyotrophic lateral sclerosis, and syringomyelia. Choreoathetoid movements in cerebral diplegia.
4. Sensory system:
   (a) *Dissociated anaesthesia* – A lesion in the centre of the cord, e.g. syringomyelia, haematomyelia, intramedullary tumour, anterior spinal artery thrombosis or haemorrhage (impaired pain, temperature, touch preserved).
   (b) *Total loss of all forms of sensation* – below the segmental level in the trunk at which the transection takes place. Often there is a zone of hyperaesthesia in the skin area supplied by the segment of the spinal cord immediately above the lesion.
   (c) *Signs of posterior column affection* – Sensory ataxia, Romberg's sign, loss of vibration and position sense with normal tactile and pain sensations in subacute combined degeneration and injury or compression of cord.
   (d) *Only lateral column affection (Pure motor spastic paraplegia)* (Table 53).
   (e) *Postero-lateral columns affection (Sensory motor spinal cord disorders)* – (i) Subacute combined degeneration, (ii) Multiple sclerosis, (iii) Syringomyelia, (iv) Compression myelitis, (v) Haematomyelia and myelomalacia, (vi) Radiation myelitis, (vii) Pellagra.
   (f) *Radicular spinal syndrome* – Signs of spinal cord compression associated with root pains, segmental sensory changes or motor disturbance and spinal tenderness all occurring at level of lesion – spinal arachnoiditis.
5. Reflexes:
   (a) *Absent knee and ankle jerks with extensor plantar* (Table 54)
   (b) *Inversion of the radial reflex* – long-standing cervical disc protrusion.
   (c) *Paraplegia with loss of deep reflexes*
      1. State of spinal shock.

Table 52: Paraplegia with optic atrophy

1. Hereditary ataxias – Friedreich's, Sanger Brown.
2. Demyelinating – Multiple sclerosis.
3. Infections – TB, syphilis, arachnoiditis.
4. Deficiency – Subacute combined degeneration, pellagra.
5. Vascular – Eale's disease.
6. Toxic – Alcohol, SMON.
7. Miscellaneous – Metastasis, Paget's disease of bone.
8. Neuromyelitis optica (Aquaporin antibodies).

Table 53: Causes of pure motor spastic paraplegia

• Amyotrophic lateral sclerosis.
• Anteriorly placed extradural compression, e.g. TB spine.
• Vascular lesions like thrombosis or haemorrhage in which sensory function has recovered.
• Primary lateral sclerosis.
• Cerebral palsy.
• Lathyrism.
• Familial spastic paraplegia.

Table 54: Paraplegias with absent ankle jerks with extensor plantar

• Subacute combined degeneration.
• Friedreich's ataxia.
• State of spinal shock.
• Meningeal carcinomatosis.
• Coexisting lumbar and cervical spondylosis.
• Conus medullaris lesion.
• Epiconus lesion.
• Spinal arachnoiditis.
• Taboparesis.

2. Spinal artery thrombosis/hemorrhage.
3. Associated radiculitis

6. Sphincters:
   (a) *Spinal bladder* from damage to spinal cord by trauma, cord tumour or multiple sclerosis.
   (b) *Autonomous bladder* in cauda equina lesions.
   (c) *Sensory bladder* in subacute combined degeneration and multiple sclerosis.
7. Trophic changes – Syringomyelia.
8. Gait:
   (a) Ataxic in SCD and MS.
   (b) Scissor gait in cerebral diplegia.
   (c) In lathyrism patient walks with stiff legs bent at knees and advancing limb strongly abducted and dragged forward with the toes reaching the ground first.
9. Spine – Deformity, tenderness and rigidity in TB spine. Kyphoscoliosis in syringomyelia and hereditary ataxias. Percussion tenderness in radicular spinal syndrome, TB spine.
10. Other findings:
   - *Other signs of syphilitic infection* in spinal syphilis.
   - *Anaemia and tenderness of calf muscles* in subacute combined degeneration.
   - *Constitutional symptoms* or evidence of tuberculosis elsewhere in the body in Pott's disease.
   - *Painful, stiff neck* with pain in arms with spastic weakness of legs in elderly persons should suggest cervical spondylotic myelopathy.
   - *Symptoms due to primary disease,* e.g. leukaemia (secondary deposits).
   - *Symptoms of increased intracranial pressure* in intracranial tumour.
   - *Short neck with a low hair line* and limitation of rotation of neck in chronic progressive myelopathy complicating craniovertebral anomaly.
   - *Lhermitte's sign* – may be positive in multiple sclerosis, craniovertebral anomaly, cervical spondylosis or cervical cord injuries, and subacute combined degeneration. The patient complains of sudden, transient, electric shock feeling spreading down the body when he flexes the head forward.
   - *Pes cavus* in Friedreich's ataxia and familial spastic paraplegia.
   - *Mottling of teeth* in fluorosis.

III. Investigations

1. CSF – Routine, serological tests for diagnosis of spinal syphilis. *Froin's syndrome* – In spinal block – (a) Xanthochromic fluid. (b) Increase in proteins as a result of which the fluid may coagulate spontaneously. (c) Slight or no increase of cells.
2. Imaging –
   (a) *Plain X-ray of vertebral column* – Changes of TB spine, herniated intervertebral disc, secondary deposits, fracture dislocation. In spinal tumour increase of distance between pedicles or erosion of vertebra. X-rays of cervical spine for spondylosis and cervicovertebral junction for dislocation of atlantoaxial joints.
   (b) *MRI* – is investigation of choice for cord compression.
   (c) *CT scan* – for detecting bony abnormalities of vertebral column – Vertebral osteomyelitis, metastasis, myeloma, osteosclerosis.
   (d) *Chest radiograph* – Lung carcinoma is a common primary causing metastatic spinal disease.
   (e) *Cerebral angiography* – if suspicion of expanding mass or vascular abnormality.
3. Blood – (i) Megaloblastic anaemia in subacute combined degeneration. (ii) Treponemal antibodies in spinal syphilis. (iii) Protein electrophoresis for multiple myeloma. (iv) Prostate specific antigen for prostatic malignancy if indicated.

4. Gastric analysis – Pentagastrin-fast achlorhydria with maximum histamine stimulation in SCD.
5. Fundus – Papilloedema in intracranial tumour. Temporal pallor in multiple sclerosis. Hydrocephalus, cerebral venous sinus thrombosis with parasagittal venous haemorrhagic infarcts.
6. Urine – for fluorine estimation in endemic fluorosis.
7. Therapeutic test – If suspected cervical disc degeneration, restriction of neck movements by rest or by wearing a collar for few weeks will often produce marked improvement in walking.

D.D. of Flaccid paraplegias (Paraparesis)

1. ***Poliomyelitis*** – (i) Acute onset with possibly signs of meningeal irritation. (ii) Muscular weakness and flaccid paralysis of scattered muscle groups. (iii) Not bilaterally symmetrical.
2. ***Peripheral neuritis*** – (i) Numbness and tingling at onset. (ii) Tenderness of calf muscles. (iii) Glove and stocking type of anaesthesia. (iv) Vasomotor and trophic changes – oedema, dryness, desquamation. (v) Bilaterally symmetrical paresis.
3. ***Guillain-Barre syndrome*** – (i) Preceding viral illness. (ii) Weakness usually starting in lower limbs, increases in severity over next few days and then ascends up to involve trunk muscles, upper limbs and in some cases neck, face and bulbar muscles. (iii) Areflexia is the key to diagnosis.
4. ***Cauda equina lesions*** (Any lesion in spinal canal below T10 can cause cauda equina syndrome) – (a) Lateral cauda equina syndrome (e.g. neurofibroma) – Anterior thigh pain, weakness of quadriceps and absent knee jerk. In case of high lesion extensor plantar response. (b) Midline cauda lesion from within (Conus lesion) – (e.g. ependymoma (Fig. 51), dermoid or lipoma) – Rectal and genital pain, micturition disturbances and impotence. Saddle anaesthesia. Symmetrical findings. (c) Midline lesion from outside (e.g. disc) – Signs of bilateral lumbar and sacral root involvement.
5. ***Lumbar disc syndrome*** – Paraplegia rare. (i) History of trauma may be obtained. (ii) Initial phase of pain in lumbar region. (iii) Radiation of pain to buttocks and back of thigh. (iv) Pain often aggravated by coughing. (v) Impairment of spinal movements. (vi) Impairment of sensation over dorsum of foot common.
6. ***Lumbar disc stenosis*** – Constriction of lumbosacral spinal canal can produce symptoms due to direct compression or vascular insufficiency (syndrome of intermittent claudication of cauda equina). Presentation can be unremitting with backache and radicular radiation, or more commonly, with intermittent symptoms such as transient weakness or numbness as a result of exertion or hyperextension of lumbar spine. To ease symptoms, patient may adopt stooping posture when walking. Absent reflexes, sensory loss, weakness and impaired straight leg raising may be demonstrated only after exertion. CT scan myelography – Characteristic angular or trefoil appearance of neural canal or MRI.

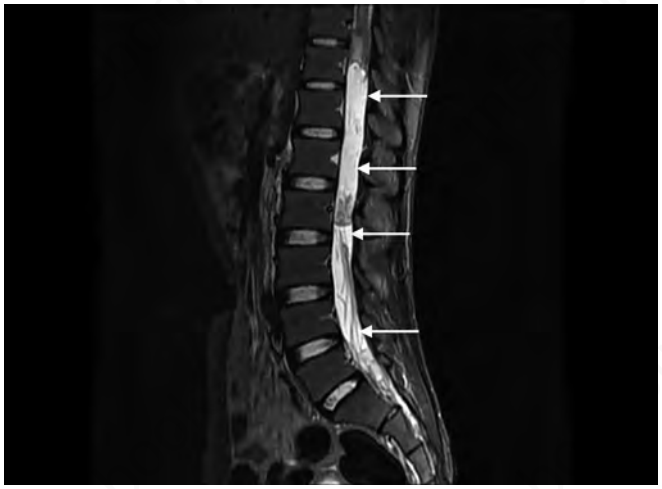


Fig. 51: Ependymoma filum terminale (arrows)

7. ***Tabes dorsalis*** – (i) Lightning pains. (ii) Absent ankle and knee jerks. (iii) Pupillary changes. (iv) Positive Romberg's sign.
8. ***Friedreich's ataxia*** – (i) Heredofamilial. (ii) Age – usually young, 10–15 years. (iii) Cerebellar signs – Nystagmus, ataxic dysarthria or scanning speech, ataxia. (iv) Pyramidal signs – Absent abdominal reflexes, extensor plantars. (v) Posterior column involvement – Loss of tendon reflexes. (vi) Deformities – Pes cavus and scoliosis.
9. ***Peroneal muscular atrophy*** – (i) Usually young adults. (ii) Muscular wasting in lower limbs; muscles involved transversely (fat bottle or inverted champagne bottle appearance). (iii) High steppage gait and clubbed feet.
10. ***Hysterical*** – (i) Paralysis generally preceded by pain or discomfort in the limbs. (ii) Muscular wasting may occur after some time due to disuse. (iii) Stocking type of anaesthesia common. Sharply demarcated sensory loss. (iv) Patient can often move legs normally when lying or sitting, but collapses at once when he tries to stand or walk (astasia abasia).

11. ***Distal myopathy of Welander*** – Very rare. Slowly progressive, predominantly distal wasting and weakness.

COMPRESSION OF THE SPINAL CORD AND ROOT COMPRESSION

Classification: There are many possible classifications of compression based on location (extradural or intradural), disease type (congenital, acquired, inflammatory, infective, neoplastic, degenerative or traumatic) or timing of onset (acute or chronic).

Location

Extradural compression – Common – disc prolapse or spondylosis, metastatic disease and spinal trauma.

Intradural compression may be situated within the cord substance (intramedullary) or on the surface (extramedullary). It is less common than extradural compression.

- Intradural extramedullary lesions are mainly tumors and almost always benign and include meningiomas and neurofibromas.
- Intradural intramedullary lesions are less common; the principal tumors are astrocytoma (Fig. 52) and ependymoma.

Table 55 lists the causes of compression of cord.

Onset – May be acute (e.g. lumbar central disc causing cauda equina syndrome, traumatic injury to the spine) or chronic (e.g. a slow-growing benign tumour such as meningioma or neurofibroma), or sometime acute-on-chronic (e.g. metastatic breast carcinoma complicated by vertebral body collapse).

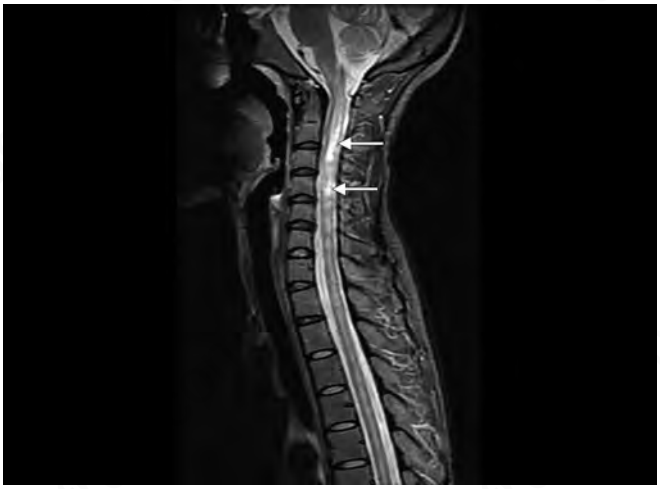


Fig. 52: MRI STIR image showing astrocytoma in cervical cord (arrows)

Clinical Features

Acute cord compression syndrome is manifested by complete motor paralysis (corticospinal function) and sensory anaesthesia (spinothalamic function). Damage is primarily in the anterior two-thirds of the cord related to vascular insufficiency. Motor loss is often greater in lower legs than in arms. Marked spinal pain and tenderness.

Brown-Sequard syndrome results from hemisection of the spinal cord with unilateral damage to spinothalamic and corticospinal tracts, and resultant loss of ipsilateral motor and dorsal column function and of contralateral pain and temperature sensation. It often results from penetrating trauma or unilateral facet fracture or dislocation or demyelination.

Table 55: Causes of compression

Congenital
• Spinal dysraphism (spina bifida, diastematomyelia, tethered cord)
• Dwarfing syndromes (achondroplasia, Morquio's syndrome, spondyloepiphyseal dysplasia)
• Chiari malformation (cerebellar ectopia)
• Vertebral body malformation (hemivertebra)
Acquired
Traumatic
• Fracture dislocation
Infective – Osteomyelitis of vertebrae
• Bacterial
• Fungal
• Tuberculous
Inflammatory – Demyelinating
• Multiple sclerosis
• Sarcoid
• Rheumatoid arthritis
Neoplastic
• Benign
• Malignant (primary or secondary)
Biochemical
• Paget's disease
Endocrine
• Hyperparathyroidism (Brown's tumour)
• Osteoporosis collapse
Degenerative
• Cervical spondylosis (myelopathy or radiculopathy)
• Lumbar disc
• Spondylolisthesis
• Lumbar sacral stenosis

Central cord syndrome is often associated with extension injury to an osteoarthritic spine. This results in proportionally greater loss of motor function in the arms than in the legs, with variable sensory sparing ('man in a barrel'). Fibres responsible for lower extremity motor and sensory functions are located in the most peripheral parts of the cord, whereas fibres controlling the upper extremity and voluntary bowel and bladder function are more centrally located. Sacral tracts are located on the periphery of the cord and are usually spared from injury. Impact damage to the grey matter, produced by the 'pincer' effect of osteophytes anteriorly and infolded ligamentum flavum posteriorly, produces severe lower motor neuron paralysis of fingers, hands and arms. Bladder and bowel function may also be lost. "Dissociated sensory" loss is seen.

Cauda equina syndrome. The subarachnoid space extends in a dural arachnoid sheath around each dorsal and ventral route, roughly to the level of union of the roots. A myelomere (the segment of cord from which a nerve root arises) lies one or two levels above the same number vertebral body between C_2 and T_{10}. Below the inferior end of the cord, the dural-arachnoid sac contains a leash of nerve roots; this complex constitutes the cauda equina. When examining patients who have cauda equina syndrome, it is important to assess saddle anaesthesia, rectal tone, bulbocavernous reflex and sacral sparing. Urinary retention, incontinence is the most common finding.

Localization of Segmental Level

1. **Pyramidal system** –
   - Spasticity of all four limbs – lesion above C_4 cord segment.
   - Spasticity of lower limbs plus flaccid weakness of scattered muscles of upper limbs – lesion of cervical enlargement (C_5-T_2).
   - Spasticity of lower limbs alone – lesions of thoracic cord (T_2-L_1).
   - Irregular spasticity of lower limbs plus flaccid weakness of scattered muscles of lower limbs – lesion of lumbosacral enlargement (L_2-S_2).
2. **Sensory symptoms** – Hyperaesthesia and hyperalgesia at level of lesion, analgesia and thermoanaesthesia below. Radicular pain offers a clue to specific dermatome localization early in the disease process. To localise the exact vertebral level corresponding to the spinal compression, for upper cervical same as cords level, for the lower cervical vertebrae add 1, for dorsal 1-6 add 2 and for dorsal 7-9 add 3. The 12th dorsal arch overlies lumbar 5.

   The testing of vibration sense is valuable in ascertaining the level of a lesion which affects the posterior columns. The tuning fork is applied to the bony prominences from below upwards until the level is determined at which it is felt.
3. **Reflexes** – Deep reflexes below the level of the lesion are exaggerated, and those corresponding to the level of lesion lost, e.g. lesion of $C_{5/6}$ cervical will cause loss of biceps and supinator jerks but exaggeration of triceps (inverted radial reflex).
4. **Imaging** – (i) *Plain radiograph* – in spinal tumour may show any of the following – (a) Localised destruction of the vertebra or vertebrae. (b) Changes in contour of or separation of pedicles. (c) Distortion of paraspinal tissues by tumours (frequently neurofibroma) which extend through the inter-vertebral foramen. (d) Proliferation of bone – rare except in osteomas and sarcomas, occasionally in haemangioma. (e) Presence of calcification occasionally in meningiomas. (ii) *MRI* – is the most useful investigation and has replaced myelography. It shows the degree and source of compression of neural structures. Discs are well visualized. It readily demonstrates fractures, inflammatory changes and metastatic disease, including microdeposits. (iii) *CT* – with bone windows provides superior information about osseous integrity. CT scan can be helpful in surgical planning.
5. **Other investigations** –
   - Urine – microscopy, culture and sensitivity for infection and urinalysis for Bence-Jones protein (myeloma)
   - Full blood count, ESR (marker for infection/malignancy). Macrocytes in B_{12} deficiency.
   - Routine biochemistry including calcium, liver and bone enzymes and tumour markers.

Relation of Source of Compression to Cord

1. Vertebral causes

Table 56 gives localization signs to various levels of cord compression.

2. Intraspinal tumours

Table 57 differentiates between extramedullary intradural and intramedullary cord lesion.

Table 56: Localization signs to various levels of cord compression

Cord segment	*Clinical features*	*Muscles paralysed*	*Reflexes*
C 3-4	Pain in neck and occiput. Pain, paraesthesia and weakness in upper limbs early. Relative anaesthesia of face. Quadriplegia.	Lower part of trapezius, supraspinati and infraspinati. Muscles of upper limbs. Diaphragm.	
C 5	Quadriplegia.	Deltoid, biceps, brachialis, rhomboids and supinator	Biceps (C5-6) and Supinator (C5-6) diminished or lost. Inversion of the radial reflex. Triceps ++ brisk
C 7	Paraplegia	Triceps and extensors of wrist and fingers	Triceps (C-7) lost.
C 8-D1	Spastic paralysis of trunk and lower limbs. Paralysis of ocular sympathetic sometimes.	Flexors of wrist and fingers and small muscles of hand.	Tendon reflexes in upper limbs normal, in lower limbs exaggerated.
D 6	Spastic paralysis of muscles of abdomen and lower limbs	Intercostals, upper and lower rectus abdominals, oblique abdominals	Epigastric (C-6-8) lost.
D 9-10	Spastic paraplegia.	Lower halves of rectus abdominis.	Upper abdominals present. Lower abdominals lost.
D 12-L1	Spastic paraplegia.	Lower fibres of oblique abdominis, transversalis and iliopsoas.	Abdominals present. Cremasteric (L1-2) lost.
L 3-4	Spastic paraplegia.	Paralysis of external sphincter.	Anal and bulbocavernous reflexes lost. Deep reflexes normal.
S 1-2	Flexion of hip, adduction of thigh, extension of knee and dorsiflexion of foot possible, all other movements in the lower extremities weak.	Glutei, calf muscles, anterior tibial, and peroneal, small muscles of foot	Knee jerks present. Ankle jerks lost. Plantar reflexes lost.
S 3-4	No paraplegia. Retention of urine and faeces.	Quadriceps, adductors of hip.	Knee jerks (L2-4) lost. Ankle jerks (S1-2) brisk
Cauda equina	(i) Whole cauda – Anaesthesia below the folds of the groins including genitals. Loss of control of bladder and rectum.	Paralysis of lower limbs.	Absent deep reflexes.
	(ii) Upper sacral and L5 – Sensory loss over front and posterior and outer aspect of thigh.	Paralysis of glutei, hamstrings, and all muscles below the knees.	Knee jerks present. Ankle jerks lost.
	(iii) Below S2 –Saddle shaped area of anaesthesia. Incontinence of urine and faeces.	No paralysis of lower limbs.	All reflexes in lower limbs normal.
	(iv) S 4-5 and coccygeal roots – Anaesthesia of anus and rectum.	Paralysis of levator ani.	

Table 57: Differences between extramedullary intradural and intramedullary cord lesion

Extramedullary intradural	*Intramedullary (Intrinsic lesions of spinal cord)*
1. Radicular pains common.	1. Radicular pains rare.
2. Paraesthesia rare until late.	2. Paraesthesia occur in all stages.
3. Muscle fasciculations rare.	3. Muscle fasciculations common.

Contd...

Contd...

Extramedullary intradural	*Intramedullary (Intrinsic lesions of spinal cord)*
4. No dissociated loss of sensibility.	4. Dissociation of sensations common.
5. Bladder and rectal disturbances late.	5. Bladder and rectal disturbances early.
6. Rising level of sensory disturbances as peripheral tracts more affected.	6. Descending level of sensory disturbances.
7. No sacral sparing.	7. Sacral sparing.
8. Brown-Sequard syndrome may occur.	8. Persistent Brown-Sequard syndrome very rare.
9. Spasticity and other pyramidal signs pronounced.	9. Spasticity less pronounced.
10. Little or no muscle atrophy.	10. Characterised by muscle atrophy.
11. Trophic skin changes absent.	11. Trophic skin changes common.
12. Vertebral column may be sensitive to local pressure.	12. No local tenderness of spine.
13. Spinal fluid changes frequent.	13. Spinal fluid changes rare.

CRANIOCERVICAL ANOMALIES

Clinical Features

Compression of the area of foramen magnum may present with:

1. Syringomyelia.
2. Occipital and nuchal pain and stiffness.
3. Occult hydrocephalus.
4. Nystagmus, ataxia and facial sensory loss.
5. Nuchal paraesthesiae and pseudo-athetosis in fingers.
6. Weakness and atrophy of neck and shoulder girdle.
7. Spastic tetraparesis. Evidence of pyramidal tract affection in all four limbs. Paraesthesiae either confined to upper limbs or involving all four limbs.

Clinical Entities

1. ***Atlantoaxial subluxation*** –

   Causes – Separation of odontoid process of axis may be due to occipitalization or other developmental anomalies, ankylosing spondylitis, or rheumatoid arthritis or trauma. *Associated conditions* – (i) Spinal – Syringomyelia, hydromyelia, spina bifida. (ii) Cranial – Hydrocephalus. (iii) Others – Anomalies of cardiovascular, GI and genitourinary systems.

   Clinical features – Dislocation with resultant ischemia in vertebrobasilar area may produce transitory attacks of loss of consciousness, blurring of vision or blindness, and pyramidal weakness, or tetraplegia. Delayed myelopathy may follow after some years. Other features include low hair line, short neck and restricted neck movements (Feil's triad). Dysplastic face, associated congenital anomalies and absence of cranial nerve palsies. *Diagnosis* – is made from radiographs of neck in flexion and extension.

   Treatment – Surgical fusion of atlantoaxial joint.

2. ***Basilar invagination*** – Displacement of dense of axis into foramen magnum. Usually presents as picture of posterior fossa lesion. *Clinical features* – Lower cranial nerve palsies, cerebellar signs (pyramidal dysfunction), signs of increased intracranial pressure. *Radiography* –Dense of axis is seen to extend above a line drawn from the posterior end of hard palate to posterior tip of foramen magnum (Figs. 53 and 54).

3. ***Occipitalization or fusion of other cervical vertebrae*** (Block vertebrae) – (Klippel-Feil anomaly) – Usually asymptomatic. Signs due to other associated anomalies. Feil's triad seen.

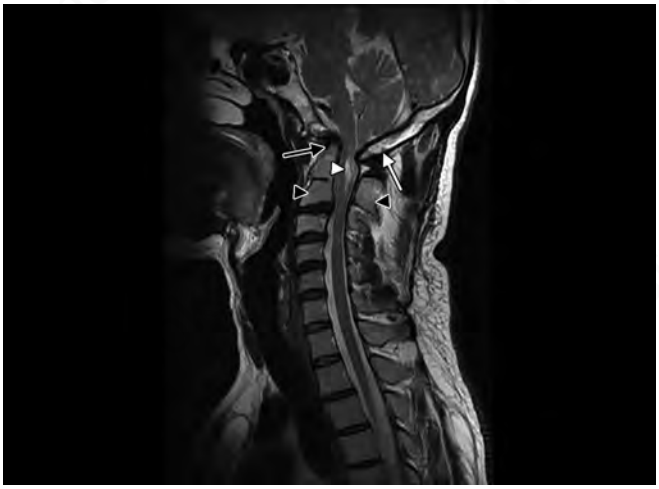


Fig. 53: MRI showing vertebro-basilar anomaly with atlanto-occipital fusion (white arrow), basilar invagination (black arrow), C2-C3 vertebral fusion (black arrowheads) and syrinx formation (white arrowhead)

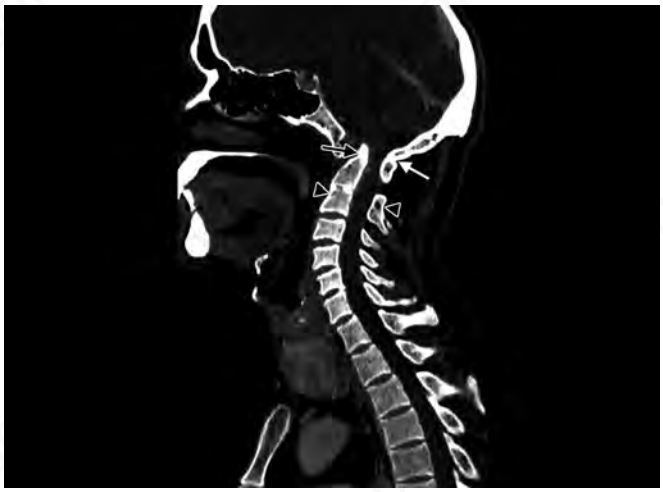


Fig. 54: CT scan showing vertebro-basilar anomaly with atlanto-occipital fusion (white arrow), basilar invagination (black arrow) and C2-C3 vertebral fusion (black arrowheads)

4. ***Arnold-Chiari malformation*** – The medulla and cerebellum are elongated and extend down through the foramen magnum. Usually presents with cerebellar signs and syringomyelia or syringobulbia-like clinical picture. Spina bifida frequent.

NON-COMPRESSIVE SPINAL CORD DISORDERS

Table 58 gives causes of non-compressive myelopathy.

Transverse myelitis reflects several pathological processes, all of which present with monophasic acute cord disturbance with bilateral involvement and segmental level. It can be acute or subacute. Table 59 for the causes of transverse myelitis.

Vascular - Thrombosis of spinal arteries, spinal A-V malformation, vasculitis due to heroine.

Clinical Features

1. At or below the level of involvement – neuropathic pain in the midline or deeper aching pain or in a dermatomal distribution (radicular pain or burning sensation), this giving a clue to the anatomical level of the lesion. Numbness and tingling sensation in the legs with diminution in pain and sensation.
2. Muscle weakness, flaccid paralysis followed by spasticity.
3. Lhermitte's sign because of demyelination
4. Sphincter impairment. Loss of bladder and bowel disturbances.

Table 58: Causes of non-compressive myelopathy

Vascular
- Infarction
- Hemorrhage
- A-V malformation
- Hypercoagulable states

Heredodegenerative
- Spinal muscular atrophy
- Hereditary spastic paraparesis
- Friedreich's ataxia
- Abetalipoproteinaemia
- X-linked adrenoleukodystrophy

Transverse myelopathy
- Multiple sclerosis
- Collagen vascular disorders
- Viral infections (e.g. herpes simplex virus)
- Myelitis – Transverse myelitis

Infective
- Syphilis, HIV, HTLV-I

Nutritional
- Subacute combined degeneration
- Vitamin E deficiency, copper deficiency

Anterior horn cell disease – ALS, PLS

Tropical
- Lathyrism, konzo, tropical ataxic neuropathy

Table 59: Causes of transverse myelitis

- Viral – Herpes simplex, EB virus, cytomegalo viruses, enteroviruses, influenza, HIV, human T cell leukaemia virus
- Post-vaccine (rabies)
- Autoimmune disease - SLE, Sjogren's syndrome systemic sclerosis
- Multiple sclerosis
- Neuromyelitis optica (Devic's disease)

Diagnosis

1. CT, MRI
2. CSF – Shows monocytes increased with elevated IgG index.
3. Tests for remedial aetiology – chest X-ray, serological tests, HIV, antinuclear antibodies.

Multiple sclerosis – Spinal cord involvement in the form of transverse myelitis or a partial cord syndrome is a presenting feature in about one-third of patients, and is almost inevitable once the disease is established (Refer).

VASCULAR NON-COMPRESSIVE SPINAL CORD DISORDERS

Infarction – The anterior cord is more vulnerable than the posterior particularly in the watershed area of the artery of Adamkiewicz (T8-L2). Cord infarction is characterized by sudden onset of pain, flaccid paraparesis and urinary retention, with later spasticity and hyper-reflexia. Anterior spinal artery thrombosis.

Arteriovenous malformation (AVM) – Spinal AVM is usually congenital; it may be associated with other vascular anomalies. The most common form usually occurs below the level of T3 and comprises abnormal vessels that are partly extramedullary and are fed by durally located fistulas. Typically, a gradually evolving mixed upper and lower motor neuron defect is seen, associated with sensory disturbances and sometimes sphincter involvement.

HEREDODEGENERATIVE SPINAL CORD DISEASES

Spinal muscular atrophy (SMA) – The hallmarks are progressive weakness, hypotonia and generalized muscular atrophy secondary to degeneration of anterior horn cells or loss of bulbar motor nuclei. (a) *In acute infantile SMA,* onset of symptoms before 6 months and occasionally from birth. Motor 'milestones' are delayed and death occurs before 2 years. (b) *Late onset SMA* (Kugelberg-Welander) – Onset of symptoms is typically by 3 years. Weakness and wasting involving face, tongue and proximal musculature, including diaphragmatic weakness is seen, and scoliosis and contractures are common. It is an autosomal recessive disorder.

Hereditary spastic paresis – Symptoms may develop at any age usually manifesting as difficulty in walking. Examination shows spasticity, and hyperreflexia with extensor plantars. Weakness is usually not marked. Mild sensory impairment and pes cavus may be found. It is an autosomal dominant disorder.

Friedreich's ataxia – (Refer)

INFECTIVE NON-COMPRESSIVE SPINAL CORD DISORDERS

Syphilis – (a) In meningovascular syphilis, leptomeningeal exudation with granulomata and endarteritis produces subacute or chronic progressive spastic paraparesis. Radicular pain is common. Dorsal column sensory impairment leads to sensory ataxia. (b) Tabes dorsalis.

HIV – Myelitis may occur as part of seroconversion stage of infection. The most common single cause of myelopathy in HIV is vacuolar myelopathy, a late disease marker occurring when CD4 count falls below 200/µl. It produces slowly progressive spastic paraparesis, extensor plantar responses, sensory ataxia and sphincter disturbance. The mechanism of myelopathy is unknown, but may involve activated microglial neurotoxicity, gp120 protein myelin toxicity or cellular vitamin B_{12} deficiency.

Nutritional – Subacute combined degeneration.

Tropical non-progressive spinal disorders

Lathyrism is an epidemic syndrome due to increased consumption (200-300 gm/day for 3 months) of the legume *Lathyrus sativus,* which contains the excitatory neurotoxin β-N-oxalyl-amino-L-alanine. Early transient excitatory autonomic phenomena (e.g. enuresis, urinary frequency, nocturnal ejaculation) are followed by spastic paraparesis with disproportionate spasticity.

Konzo and tropical ataxic neuropathy due to inadequate preparation of Cassava root fails to remove natural cyanogenic glycosides. Clinical features are similar to those of lathyrism. In tropical ataxic neuropathy, dorsal column degeneration, sensory ataxia, hyporeflexia, optic atrophy and sensorineural deafness are seen.

LEVEL OF DISEASE

1. Cervical myelitis –
   (a) *Motor symptoms* – Paralysis of upper and lower extremities, if high cervical, death in few days.
   (b) *Sensory* – Hyperaesthesia and root pains in the segmental areas with diminished sensations below.
   (c) *Reflexes* – All reflexes usually lost at onset. Later tendon reflexes return in lower extremities and plantars become extensor. In complete recovery, the abdominal and cremasteric reflexes are usually lost to resume normal activity later.
   (d) *Sphincters* – Retention of urine and faeces. After about a fortnight, automatic bladder. Sphincter function usually returns early. Priapism often present.
   (e) *Trophic changes* – Likely to occur. Oedema and bedsores. Cystitis.
2. Dorsal – Commonest form. Symptoms same as cervical but no involvement of arms. Priapism common. Girdle pain and hyperaesthetic zone between ensiform cartilage and pubes. Retention or intermittent incontinence of urine.
3. Lumbar cord and conus – Paralysis of legs partly of upper and mainly of lower motor neuron; knee jerks absent (upper lumbar segment involved). Plantar reflex almost always abolished. Incontinence of urine and faeces. No priapism.

COURSE

Paraplegia in extension – In acute myelitis at the onset, all the reflexes are lost below the level of the lesion – stage of flaccidity or spinal shock. After about 3 weeks, spasticity and increased reflexes develop. Extensor muscles are spastic. Hip extended and adducted, knee extended and feet plantar flexed. At times when the stage of reflex activity supervenes, there may be spasms of the limbs, automatic bladder contraction, and excessive sweating, due to uncontrolled activity of the spinal centres in response to cutaneous stimuli (mass reflex).

Paraplegia in flexion – occurs after a complete transverse lesion as soon as the stage of spinal shock has passed; or in cases of diffuse spinal lesions, follows paraplegia-in-extension after the extrapyramidal motor tracts have also become involved. Thigh and knee flexed, feet dorsiflexed. Flexor spasms occur in the lower limbs which in severe cases become fixed in an attitude of flexion.

MANAGEMENT

General – Symptomatic and rehabilitative with the aim of preserving function and avoiding complications of contracture, pressure sores and automatic dysreflexia. Good skin care. Passive stretching exercises and physiotherapy aimed at truncal support and optimizing activity in functioning muscle groups are adjuncts to an antispasmodic (baclofen, tiazanidine, dantrolene). When spasticity is severe, baclofen can be given intrathecally, or botulinum toxin can be used to weaken problematic muscle groups.

Functional independence can be maximized by occupational therapy. Detrusor instability may be helped by oxybutynin, but intermittent or permanent suprapubic catheterization may be necessary.

Specific – e.g. IV acyclovir 10 mg/kg 8-hourly in herpetic transverse myelitis. A short pulse of 3 days high-dose i.v. methyl prednisolone, 0.75-1 g/day, may reduce the time to recovery in multiple sclerosis. AVMs may be selectively embolized, and are occasionally ligated surgically. Development of vascular myelopathy in HIV may be prevented by early antiretroviral therapy.

MULTIPLE SCLEROSIS

Multiple sclerosis is an inflammatory demyelinating disease of CNS (brain and spinal cord) that is disseminated in time and space (i.e. neuroanatomical location).

Pathogenesis

An acute MS plaque develops when primed leucocytes cross the blood-brain barrier into the brain and activate macrophages. Inflammation is initiated and myelin is stripped off nearby nerve axons. Demyelinated axons lose the ability to conduct nerve impulses in normal manner, and axonal conduction is further impeded by the direct effect of soluble inflammatory mediators such as nitric oxide.

The rapid disappearance of these mediators when inflammation subsides may account for the rapid resolution of symptoms sometimes seen after an attack. It is now recognised that axons may degenerate as a secondary response to demyelination, and the axonopathy contributes to disease progression.

Autoimmune disease – The female predominance and its weak association with specific HLA types (particularly HLA DR15 and DQ6) suggests that MS may be an autoimmune disease. In 20% of patients MS affects one other family member.

Genetic predisposition – to MS is also suggested by the racial variation in prevalence and the higher concordance risk in identical compared with non-identical twins. Hence, expression of MS probably depends on the interplay of an inherited risk (from the summation of several genes) with an environmental trigger; this may be an infective agent such as human herpes virus 6 and *Chlamydia pneumoniae.*

Clinical Features

Common Symptoms

Lhermitte's symptom – Neck flexion induces an 'electric shock' sensation running down the back, caused by a plaque in the cervical cord.

Optic neuritis – Patients experience pain in one eye, particularly on eye movement, and dimming of vision in that eye, often described as looking through a dirty window or water.

Spasticity, particularly in spinal cord lesions, may lead to stiffness, flexor spasms, cramps or spontaneous clonus.

Ataxia of the limbs may be caused by a lesion of the cerebellum or its connections, or by deafferentation from a dorsal column spinal plaque.

Fatigue is often prominent.

Neuropathic pain may occur as part of a spinal cord syndrome or alone as in symptomatic trigeminal neuralgia.

Mood disturbance – Euphoria with advanced MS, but depression is more common.

Bladder dysfunction – it can be either detrusor hyperreflexia or detrusor sphincter dyssynergia.

Table 60 gives signs of demyelinating lesions in MS according to the site of lesion.

Symptom patterns – Symptoms caused by demyelination emerge over several days, reach a plateau and then usually resolve over days or weeks. Characteristically symptoms reappear transiently or worsen with an increase in body temperature (Uhthoff phenomenon).

Depending on Clinical Course Four Subtypes

Relapsing/remitting MS (RRMS)
Secondary progressive MS (SPMS)
Primary progressive MS (PPMS)
Progressive/relapsing MS (PRMS)

1. Relapsing/remitting MS (RRMS) - accounts for 85–90% of cases at onset, characterized by discrete attacks that generally evolve over days to weeks followed by substantial or complete recovery over the ensuing weeks to months. Between attacks, patients are neurologically stable.
2. Secondary progressive MS (SPMS) - always begins as RRMS. The clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase). SPMS produces a greater amount of reduced neurologic disability than RRMS.
3. Primary progressive MS (PPMS) - patients do not experience attacks but only a steady functional decline from disease onset.
4. Progressive/relapsing MS (PRMS) overlaps PPMS and SPMS and accounts for 5% of MS patients

Table 60: Signs of demyelinating lesions in MS

Site of demyelination	*Symptoms*	*Signs*
Spinal cord	Limb weakness	Spasticity
	Lhermitte's symptom	Pyramidal weakness
	Stiff legs	Hyper-reflexia
	Sensory impairment	Absent abdominal reflexes
	Erectile dysfunction	Extensor plantars
	Urinary frequency and retention	Spinal sensory level
	Constipation	
	Flexor spasms	
Brainstem	Ataxia	Internuclear ophthalmoplegia
	Diplopia	Nystagmus
	Dysarthria	Gaze palsies
	Dysphagia	Facial sensory loss
	Facial numbness/ weakness	Rubral tremor
Cerebellum	Unsteady gait and slurred speech	Gait and limb ataxia
		Dysarthria
		Nystagmus
Optic nerve	Unilateral visual loss and painful eye movements	Relative afferent pupillary defect
		Lost colour vision/ acuity
		Optic atrophy (late sign)
Cerebrum	Poor memory	
	Personality change	Dementia (subcortical)
	Epilepsy	

Marburg's Variant of Multiple Sclerosis

Acute MS is a rare fulminant rapidly progressive demyelinating process with multiple lesions involving central hemispheres, brainstem or optic ns. Usually there are no remissions.

Differential Diagnosis

- Structural lesion, if isolated demyelinating syndromes
- Leber's hereditary optic atrophy (Bilateral optic neuropathy to the point of blindness is rare in MS).
- Progressive cerebellar symptoms may be caused by metabolic disease or inherited cerebellar ataxia
- A complete intrinsic spinal cord lesion that develops rapidly over hours (transverse myelitis) is compatible with MS, but is also recognized as a separate monophasic entity.
- Devic's neuromyelitis optica – Optic neuritis and myelopathy occur simultaneously or sequentially.
- Acute disseminated encephalomyelitis is a post-infectious illness of monophasic but multifocal CNS demyelination involving optic nerves, brainstem and spinal cord. It is usually seen in children, but may affect adults after an infection.
- Systemic lupus erythematosus – Relapsing remitting disease may be seen, but there is presence of other systemic features.
- Marburg's variant of MS – Rare, fulminant, rapidly progressive demyelinating process with multiple lesions involving cerebral hemisphere, brainstem or optic nerves.

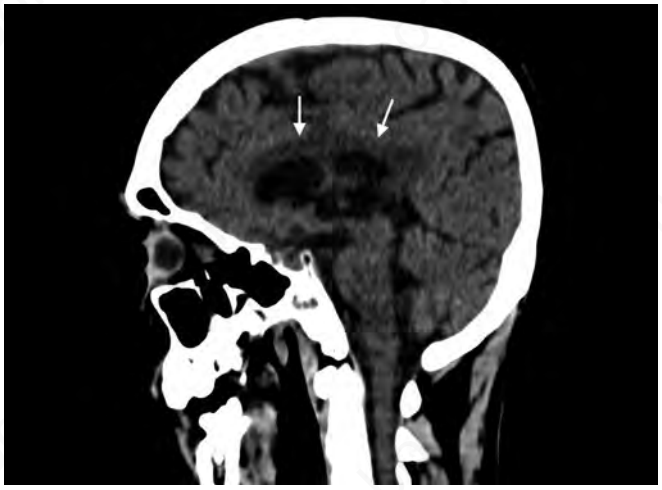


Fig. 55: CT showing degeneration of corpus callosum (arrows) suggestive of Marchiafava-Bignami syndrome

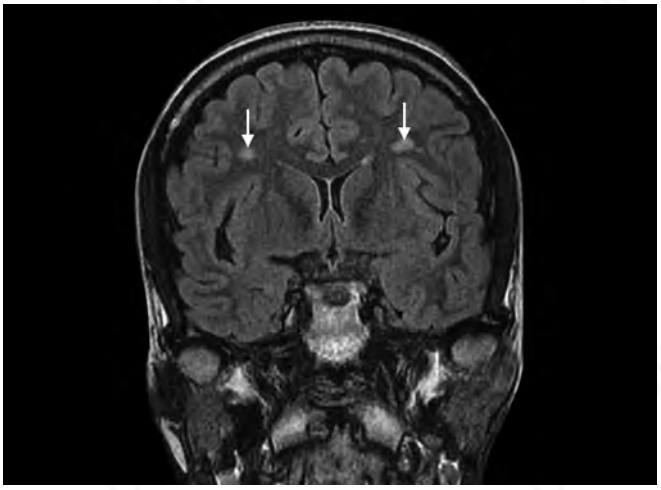


Fig. 56: MRI T2 Flair image showing demyelination

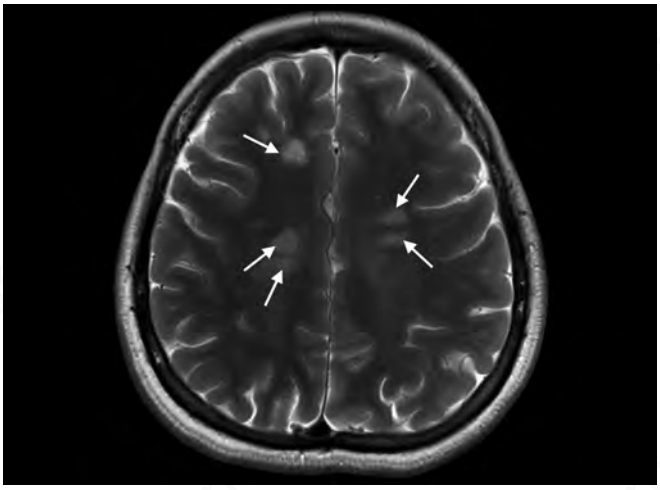


Fig. 57: MRI axial T2 image showing multiple demyelinating plaques in multiple sclerosis (arrows)

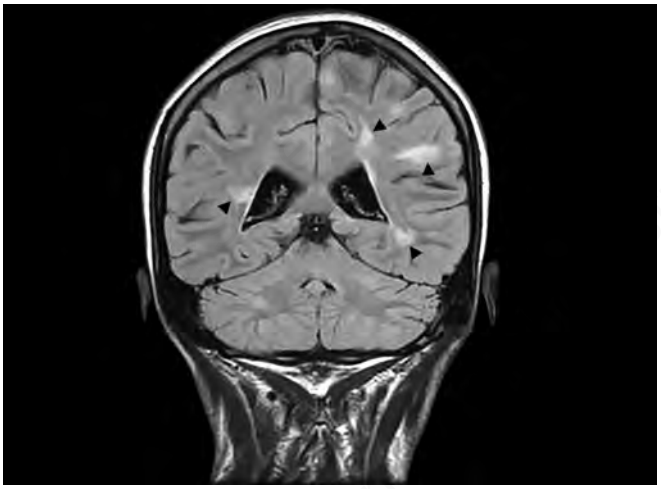


Fig. 58: MRI coronal Flair image showing multiple demyelinating plaques in multiple sclerosis (arrowheads)

- Tumefactive demyelination is a variant of MS in which plaques size is > 2 cm, on imaging studies it may be confused with intracranial tumour.
- Neurosarcoidosis often affects the optic nerve and spinal cord but there is also systemic involvement (particularly lung and skin).
- Isolated cerebral vasculitis more often causes seizures, encephalopathy, headache and fever.
- Leucodystrophies are a group of rare, inherited demyelinating disorders.
- Marchiafava-Bignami disease (MBD) is a rare condition characterized by demyelination of the corpus callosum. It is seen most often in patients with chronic alcoholism (Fig. 55).

Investigations

1. ***To demonstrate involvement of disseminated anatomical sites*** – (a) MRI most sensitively reveals asymptomatic lesions. Serial MRI demonstrates dissemination of lesions in time more rapidly than clinical events (Figs. 56 to 59). (b) Visual evoked potentials – A unilateral delay is the most sensitive index of previous subclinical optic neuritis. (c) BAER (brainstem auditory evoked responses) to demonstrate auditory pathway subclinical lesions.
2. ***To demonstrate inflammatory demyelination*** – (a) CSF: Presence of oligoclonal bands in CSF but not serum indicates inflammation confined to the CSF and is seen in 95% of patients with clinically definite

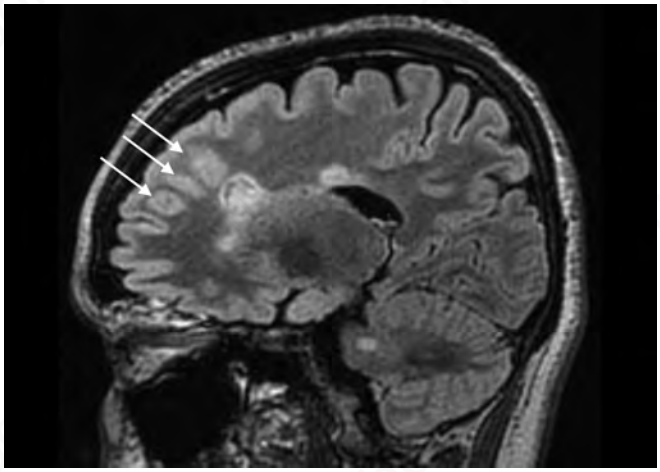


Fig. 59: MRI sagittal Flair image showing Dawson's fingers in multiple sclerosis (arrows)

MS. (b) Evoked potentials are usually delayed and their amplitude relatively preserved.

3. ***To exclude other conditions mimicking MS*** – Often structural lesions must be excluded by MRI.

Other Uses of MRI in MS

- New MRI lesions are considered 'surrogate markers' of multiple sclerosis disease activity in treatment trials.
- MRI may be used to predict the risk of MS in those who present with an isolated demyelinating event. For example, the risk of developing clinically definite MS 5 years after an episode of optic neuritis is 15% in patients with normal brain MRI, and 50% with three or more abnormal lesions on MRI at presentation.

Management

No effective curative treatment.

1. ***Treatment modifying the course of the disease***

   IFNβ, Ia, Ib – has many potential sites of action, but probably acts mainly by inhibiting the effects of pre-inflammatory cytokines on microglial activation, thus preventing amplification of the immune response. The drug is given by s.c. or i.m. injection 1–3 times weekly, and may be useful in those who suffer frequent or disabling relapses.

   Multiple sclerosis. Frequency of relapses may be reduced during pregnancy but may increase in the puerperium; overall pregnancy has little effect on the course of the illness.

   Interferon-b is not recommended during pregnancy

   Glatiramer acetate – is a mixture of synthetic polypeptides and may act by specifically blocking immune responses to myelin basic protein, an autoantigen in MS. Dose: 20 mg SC daily.

   Natalizumab - humanized monoclonal antibody directed against the α4 subunit of α4β1 integrin, a cellular adhesion molecule expressed on the surface of lym phocytes. It prevents lymphocytes from penetrating the BBB and entering the CNS. Effective in reducing the attack rate and significantly improves all measures of disease severity in MS.

   Fingolimod - is a sphingosine- 1 -phosphate (S1P) inhibitor that prevents the egress of lymphocytes from the secondary lymphoid organs such as the lymph nodes and spleen. Its mechanism of action is the trapping of lymphocytes in the periphery and inhibiting their trafficking to the CNS. It reduces the attack rate and significantly improves all measures of disease severity in MS.

   Dimethyl Fumarate (DMF) - it seems to have anti-inflammatory effects through its modulation of the expression of proinflammatory and anti-inflammatory cytokines

   Teriflunomide - active metabolite of the drug leflunomide, inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which is a key part of the pathway for de novo pyrimidine biosynthesis.

   Mitoxantrone received (from the FDA) the broadest indication of any current treatment for MS, indicated for use in SPMS, PRMS and in patients with worsening RRMS.

   Alemtuzumab - a humanized monoclonal antibody directed against the CD52 a ntigen, which is expressed on both monocytes and lymphocytes. It causes lymphocyte depletion, markedly reduced the attack rate.

2. ***Acute relapse*** – Methylprednisolone 1 g/day for 3 days or prednisolone 60 mg p.o. for 1 week, then 40 mg for 1 week, followed by 20 mg for 1 week.

3. ***Symptomatic treatment*** –

   Spasticity – (a) *Baclofen* 10 mg/day, increased to maximum 80–100 mg/day in divided doses. It acts on α-aminobutyric receptors to suppress reflex arcs that have been released from higher inhibitory control. (b) *Tizanidine* – 2 mg/day and increased slowly to maximum 20 mg/day. It acts through α2 cord receptors to moderate presynaptic release of excitatory amino acids. It is less sedating than baclofen, and associated with less muscle weakness. (c) *Dantrolene* has a direct effect on skeletal muscles and is a second line drug.

   Bladder problems – If post-micturition bladder volume is more than 100 ml, failure to empty the bladder is the primary problem and clean, intermittent catheterization is recommended. If bladder empties but stores poorly Oxybutynin 5 mg t.d.s.

   Fatigue – Amantadine may help.

   Depression – Tricyclic antidepressant.

18. DEFICIENCY DISORDERS OF THE NERVOUS SYSTEM

VITAMIN B_1 DEFICIENCY

1. Nutritional polyneuropathy (Neuritic beriberi).
2. Wernicke-korsakoff syndrome.

Wernicke's Encephalopathy – Triad of

1. *Ophthalmoplegia* – Eye signs consist of nystagmus, VIth and IIIrd nerve palsies, gaze palsies and occasionally ptosis.
2. *Ataxia.*
3. *Confusion* – in early stages followed by disorientation, drowsiness and terminal coma. Neuropathological lesions – Petechial haemorrhages in grey matter around 3rd and 4th ventricles and aqueduct of Sylvius, including the mammillary bodies.

Korsakoff's Psychosis

Korsakoff's psychosis is the permanent sequel to Wernicke's encephalopathy and is characterized by severe, irreversible loss of short-term memory, with relative sparing of other aspects of cognitive function. Some patients may confabulate. Neuropathological features are neuronal loss and gliosis, and hemosiderin-containing macrophages in the same distribution as lesions in Wernicke's encephalopathy occurs during recovery.

Nicotinic acid deficiency – Mental confusion, sometimes fits, peripheral neuritis or spinal cord lesions occasional.

Pyridoxine deficiency – 1. *Chronic convulsions* – in infancy may be due to lack of pyridoxine. 2. *Polyneuropathy* – as a complication of isoniazid treatment of tuberculosis arises from blocking of pyridoxine by the drug. 3. *Wernicke's encephalopathy.*

Pantothenic acid deficiency – *Burning feet syndrome* – Intense discomfort in feet in absence of objective sensory alteration or of motor, or tendon reflex signs.

There are two lines of evidence for this – (i) Its reproduction in human volunteers by giving them omega-methyl-pantothenic acid, an analogue of the vitamin which acts as an antagonist. (ii) Nitrofurazone, a drug used in treating trypanosomiasis, causes an acute burning feet syndrome which responds promptly to parenteral calcium pantothenate.

VITAMIN B_{12} DEFICIENCY

Types of Disorders

(a) **Cerebral type** – Symptoms cover a wide range and consist of mild disorders of mood, mental slowness, memory defect which may be severe, confusion which may be persistent or relapsing, delusions and paranoid behaviour and sometimes violent mania, visual and auditory hallucinations. Faecal and urinary incontinence in the absence of overt spinal lesions. These cerebral symptoms depend on demyelinating lesion of the white matter in the brain of the same nature as occur in the posterolateral column of the spinal cord and peripheral nerves. Optic atrophy or its precursor retrobulbar neuritis is not uncommon and may be the first manifestation, occurring predominantly in males.

(b) **Peripheral neuritis** (see Polyneuritis).

(c) **Subacute combined degeneration.**

Aetiology – (i) Age – 40–60. (ii) Both sexes. (iii) Familial incidence known. (iv) Associated conditions – usually pernicious anaemia (Vitamin B_{12} deficiency). Rarely as a result of carcinoma stomach, gastrectomy and gastroenterostomy, steatorrhoea or malnutrition from protein deficiency. Condition is characterized by decrease in myelin synthesis and demyelination of corticospinal tracts and posterior columns.

Clinical Features

Onset - usually gradual, sometimes rapid.

1. *Subjective sensory disturbances* – Paraesthesia – Tingling and numbness in toes, tips of fingers, rarely simultaneously in both upper and lower extremities. Sometimes burning or stabbing pains or even lightning pains like tabes.
2. *Objective sensory loss* – Sense of vibration, posture and passive movement affected first in lower, later in upper limbs. Glove and stocking type of superficial sensory loss. Tenderness of calf muscles.
3. *Motor symptoms* – Pyramidal weakness and ataxia develop at variable interval after onset of sensory disturbances.
4. *Reflexes* – Variable – Ankle jerks lost, knee jerks may be absent. Both exaggerated if lateral column lesion predominates. Plantars extensor.
5. *Sphincter disturbances* – First difficult or precipitate micturition, later retention of urine or incontinence. Impotence early.

6. *Mental changes* – not uncommon. Mild dementia, impaired memory. Confusional psychosis or irritability or depression.
7. *Bilateral primary optic atrophy* in 5%.

Diagnosis – Low haemoglobin, macrocytosis, high MCHC, megaloblastic bone marrow, gastric achlorhydria, serum vitamin B_{12} less than 100 pg/mL, elevated homocysteine.

Management – 1,000 mcg of vitamin B_{12} IM daily for 7–10 days, then same dose twice a week for one month, then once a fortnight to be continued for the rest of the patient's life.

Vitamin E deficiency – Impaired proprioception, sensory ataxia, areflexia.

19. EXTRAPYRAMIDAL SYNDROMES

CLINICAL MANIFESTATIONS OF LESIONS IN DIFFERENT PARTS OF EXTRAPYRAMIDAL SYSTEM

Putamen – Athetosis.
Caudate nucleus – Chorea.
Subthalamic nucleus – Hemiballismus.
Globus pallidus and substantia nigra – Parkinsonian tremor and rigidity.

PARKINSON'S DISEASE (PD)

PD is said to be present when bradykinesia and at least one of the following is present – rigidity, tremor or postural instability. Causes of parkinsonism are listed in Table 61.

Pathogenesis

The hallmark of Parkinson's disease is degeneration of melanin-containing dopaminergic neurons of the substantia nigra and typical neuronal inclusions known as Lewy bodies. The dopamine in the basal ganglia participates in a complex circuit of both excitatory and inhibitory pathways. These pathways are part of a loop that connects the cortex to the thalamus via the basal ganglia and back to the frontal cortex. This loop serves to modulate the motor system.

Parkinsonism is a common clinical presentation of different kinds of injuries to the substantia nigra.

Heredity – Twin studies have indicated a hereditary component in those in whom disease onset is before 50 years. In some families, autosomal dominant parkinsonism with features similar to Parkinson's disease occurs. In several families, a mutation has been found in the α-synuclein gene on chromosome 4. α-synuclein is found in Lewy bodies, and may participate in the abnormal precipitation of protein in a manner similar to formation of amyloid plaques in Alzheimer's disease.

Table 61: Causes of Parkinsonism

1. Idiopathic – Paralysis agitans (Parkinson's disease).
2. Post-encephalitic parkinsonism.
3. Symptomatic parkinsonism (Secondary Parkinsonism)
   (a) Trauma – Head injury.
   (b) Carbon monoxide intoxication.
   (c) Manganese and other metallic poisoning, MPTP.
   (d) Drug-induced – Reserpine, phenothiazines, haloperidol.
   (e) Cerebral arteriosclerosis (Vascular Parkinsonism).
   (f) Syphilitic mesencephalitis.
   (g) Tumours of brainstem rarely.
   (h) Tuberculosis (rare).

Toxins – MPTP an analogue of meperidine produces a syndrome almost indistinguishable from Parkinson's disease.

Viral infections – Post-encephalitic Parkinsonism.

Clinical Features

Triad of:

1. ***Tremor*** – may be first symptom; usually starts in one upper limb; characteristically tremor at rest and described as 'pill rolling'. Head may be involved. Tremors disappear during sleep.
2. ***Rigidity*** – Plastic or lead pipe, i.e. present to equal extent in opposing muscle groups and if a limb is passively moved the rigidity gives way with a series of slight jerks, or 'cog wheel' type, if combined with tremor.
3. ***Bradykinesia*** – is the cardinal feature of IPD.
   - Mask-like facies – with staring eyes.
   - Infrequent blinking.
   - Impaired ocular convergence.
   - Slow and monotonous speech.
   - Micrographia.
   - Reduced swinging of arms while walking.
   - Festinant gait.
4. Other features

Postural disturbance – Difficulty in rising from chairs or rolling over in bed, stooped posture. Disturbance of balance may be seen in the 'pull' test, performed by standing behind the patient and pulling back on the shoulders. Instead of moving the arms forward and swaying the trunk, parkinsonian patient may take steps backwards (retropulsion) or even fall back into the examiner's arms, without any attempt to maintain balance.

Gait disturbance – Reduced or absent swinging of one arm while walking is an early sign of Parkinson's disease. In more advanced cases neither arm may swing; at this stage, the stride length shortens, the trunk appears stiff and the whole body moves in one mass when the patient turns (turning *en block*). In further advanced disease, patients may appear to 'freeze', their feet seem stuck to the floor, or they may take small steps on the floor, often rising on the toes and leaning forwards. A diagnostically important point is that gait in Parkinson's disease has a narrow base, regardless of how advanced the disease.

Pain –Deep cramping sensations may be a primary symptom or secondary to levodopa.

Mental disturbances – (a) Anxiety. (b) Depression. (c) Dementia may be caused by a syndrome similar to Alzheimer's disease, frontal lobe dementia with a prominent lack of motivation, or a pattern with hallucinations in absence of medication.

Postural hypotension – can be caused by antiparkinsonian drugs. It should be considered in any patient who is falling or complains of lack of energy while walking.

Dyskinesia – in the form of writing, swinging movements of limbs and trunks are typically caused by excessive levodopa, but may occur with dopamine agonists.

*Nonmotor symptoms (*Table 62).

Investigations

(a) MRI usually normal. In some cases accumulation in substantia nigra may be visualized as T2 hypersensitivity. (b) PET – Reduced uptake in putamen. (c) SPECT – Decreased striatal metabolism.

Differential Diagnosis of Parkinson's Disease

Essential tremor – Predominantly action tremor with symmetrical onset and response to alcohol. Positive family history may be present.

Multisystem atrophy (MSA) – Progressive neurodegenerative disorder characterized clinically by combination of parkinsonism, autonomic, cerebellar or pyramidal symptoms and signs. In general patients respond poorly to levodopa or have transient response and provide an important clue to differentiate from idiopathic PD. Urinary incontinence and orthostatic symptoms occurring in a Parkinsonian patient within one year history of motor syndromes suggests diagnosis of MSA with high accuracy and their absence suggests PD.

Drug-induced Parkinsonism – Neuroleptics, metoclopramide, and calcium channel blockers. Rigidity prominent but there may also be tremor, oculogyric crises, buccolingual dyspraxia and retrocollis.

Vascular Parkinsonism (VaP) – also known as lower body parkinsonism and characterized by stepwise progression, pyramidal deficits, dementia.

Alzheimer's disease – Early, prominent dementia, particularly with dysphasia and dyspraxia.

Progressive supranuclear palsy – Early falling, eye movement abnormalities.

Hydrocephalus – Urinary incontinence, greater involvement of legs than arms, early dementia.

Table 62: Non-motor symptoms (NMS) of Parkinson's disease

Can present at any stage of the disease
- Olfactory dysfunction
- Constipation
- RME behaviour disorder
- Depression
- Dysphagia
- Sialorrhoea
- Urinary incontinence
- Cold hands and feet

Parkinsonism Plus

The term describes rare disorders in which there is Parkinsonism and evidence of a separate pathology, e.g. progressive supranuclear palsy. Other examples are multiple system atrophies such as olivopontocerebellar degeneration and primary autonomic failure (Shy-Drager syndrome).

Management

The mainstay of antiparkinsonian therapy is dopamine replacement. This may be achieved either directly with levodopa or indirectly with dopamine agonists or other drugs that enhance dopaminergic transmission.

Drugs for Parkinson's Disease

Drugs for Parkinson's disease are summarized in Table 63.

Plan of Treatment

Mild disease (Symptoms but no disability) – (a) Selegiline from time of diagnosis. Levodopa-sparing effect of the drug delays need for levodopa therapy. When treatment becomes necessary, a dopamine agonist is added. Anticholinergics and amantadine may also be added to ward off the need for levodopa, or (b) Levodopa 100 mg in combination with decarboxylase 25 mg t.d.s. or qds. (c) Anticholinergic initial treatment in patients with tremor, particularly if young. *With progress of the disease* – Levodopa/decarboxylase inhibitor 600–800 mg, and bromocriptine 20 mg (or lisuride 2 mg) in 3 or 4 divided doses. Dose of levodopa and dopamine agonists should be built up slowly.

Table 63: Drugs for Parkinson's disease

Drug	*Dose*	*Use*	*Side effects*
Carbidopa/levodopa	25 mg + 100 mg bd or tds	Most effective drug. Improves most features	Dyskinesias (generally choreoathetoid), nausea, postural hypotension, hallucinations
Carbidopa/levodopa (sustained release)	50 + 200 mg bd		
Dopamine agonists			
Bromocriptine	2.5 mg b.d., increased to 20–30 mg/day	Less effective than levodopa, but less dyskinesias. Reduced motor fluctuations because of longer half-life.	Same as levodopa plus pulmonary oedema with ergoline derivatives. Confusion
Lisuride	0.2 t.d.s. to 0.6 mg qds.		
Ropinirole	1–8 mg t.d.s., max 24 mg/d		
Pramipexole	0.5–1.5 mg t.d.s., max 4–5 mg/d		
Cabergoline	0.25–4 mg o.d.		
Anticholinergics	Varies according to preparation	May help for tremor, little use for other features	Dry mouth, blurred vision, urinary retention, constipation, hallucinations
Amantadine	100 mg bd	Useful as adjuvant therapy	Headache, nausea, dizziness, sleep disturbances
	200 mg bd		Erythromelalgia
MAO-B inhibitors			
Selegiline	5 mg/day initial, then 5 mg bd	Inhibits metabolism of dopamine. Useful for symptoms related to dyskinesias, delays need for levodopa	Insomnia (hence given after lunch), confusion, levodopa-related side effects
Rasagiline	0.5–1 mg/d	Used for motor fluctuation	
Piribedil	50–200 mg/day with meals	Dopamine antagonist As monotherapy in forms with tremor predominant Adjuvant therapy with L-dopa	Minor GI upset
Catechol-O-methyl-transferase inhibitors			
Tolcapone	100–200 mg t.d.s.	Reduces predictable motor fluctuations, less 'off' time	Most common side effects result from effective increase of levodopa – diarrhoea. Tolcapone may cause liver dysfunction
Entacapone	200 mg with each dose of levodopa to max. 2000 mg/day		

Problems in drug treatment

Nausea – Start with low doses, increased by one-half of a tablet every third day, tablet to be taken after food. Domperidone if nausea continues.

COMT inhibition (e.g. Tolcapone) is an excellent means of reducing motor fluctuations, however dyskinesias may become worse and should be used with caution in these patients.

Confusion and hallucinations. Levodopa is least likely to produce these complications. Anticholinergics, amantadine and selegiline should be withdrawn. If these persist, dopamine agonists should be minimized. If still hallucinations persist, use Clozapine 12.5–50 mg/day. Quetiapine 25–50 mg/day. (WBC count should be monitored weekly). ECT is effective in treatment of antiparkinsonian drug-induced psychosis and improves the motor features of Parkinsonism.

Postural hypotension results from a combination of the disease and the medication. If antiparkinsonian drugs cannot be reduced, use fludrocortisone and midodrine. Domperidone 20 mg t.d.s. sometimes reduces medication-induced hypotension.

'On-off' phenomenon – Late deterioration in response to L-dopa therapy may occur after 3-5 years in some patients due to loss of capacity to store dopamine (narrow therapeutic index of L-dopa). Generally this manifests as fluctuations in response at different time of the day (on-off effect). More complex fluctuations may be in the form of hour to hour changes with short periods of hypokinesia, tremor and dystonia alternating with dyskinesia and agitation. These patients should be treated with smaller more frequent doses of levodopa (e.g. 50–100 mg q2-3h) or with addition of Selegiline (10 mg/day) to prolong and potentiate L-dopa doses.

Physiotherapy and Rehabilitation

In the form of massage and passive stretching of muscles; posture and gait training, speech therapy and occupational therapy.

Surgical Treatment

(a) *Ablative*

- Thalamotomy – used for tremor. Complications include hemiparesis and dysphonia.
- Pallidotomy – Stereotactic technique of producing destructive lesions in globus pallidus interna improves all the features of Parkinson's disease including drug-induced dyskinesia.

(b) *Deep-brain stimulation*

Ablative procedures such as thalamotomy are irreversible. A similar effect can be obtained by implanting electrodes in the appropriate area and delivering a high-frequency electrical discharge via an impulse generator placed beneath the clavicle in a manner similar to a cardiac pacemaker. The advantage of stimulators include a smaller lesion and the ability to adjust the pattern of the stimulus to obtain the best response. Disadvantages include limited battery life and possibility to lead shifting and infection. When successful, patients experience marked improvement and some can become medication-free.

(c) *Adrenal medullary foetal tissue transplantation* – Transplantation of dopamine producing cells into the striatum has been shown to restore mobility.

OTHER EXTRAPYRAMIDAL SYNDROMES

Wilson's disease (Hepatolenticular Degeneration)

A disease of copper toxicosis inherited as autosomal recessive trait.

Clinical features:

(a) Micrographia and excessive drooling of saliva, later dysarthria gives way to dysphagia and movement disorders, increases in severity with gait and postural abnormalities and pyramidal signs. (b) Cirrhosis of liver. (c) Kayser-Fleischer ring. About 97% of pts. with neurological symptoms have KF ring. The rings are visible by naked eye in some and are confirmed by slit lamp examination. Similar rings may be seen with long standing cholestasis like biliary cirrhosis, chronic active hepatitis.

Biochemical features – Low serum ceruloplasmin <20 mg/dl (Table 64), (normal 25–50 mg/dL), high urinary copper excretion (usually more than 200 mcg/24 hours), hepatic copper concentration greater than 250 μg/g dry liver.

Neuroradiology – (a) Bright claustrum sign. (b) Peripheral putamen sign. (c) Ventral nucleus of thalamus sign. (d) Head of the giant panda sign. (e) CT scan may show generalized cerebral atrophy, with basal ganglia having low attenuation signals.

Treatment – (a) *Copper chelating agents* -D-penicillamine given life-long. Initially 1 g/day in 4 divided doses 45 minutes before or 2 hours after food, and Pyridoxine 25 mg/day. During first month of therapy sensitivity to penicillamine (fever, rash, granulocytopenia or thrombocytopenia) may occur. Penicillamine should be then withdrawn until the reaction has subsided. It should then be restarted at 0.25 g/day and gradually increased over 2 weeks to 1 g/day, with simultaneous administration of prednisolone 20–30 mg/day gradually tapered to zero.

Table 64: Causes of low serum ceruloplasmin level

1. New-born and infant (up to 6 months)
2. Severe malnutrition
3. Nephrotic syndrome
4. Protein-losing enteropathies
5. Congenital aceruloplasminaemia
6. Severe hepatic insufficiency
7. Acute hepatic infection

(b) Trientine if penicillamine not tolerated. It chelates copper and increases its urinary excretion. Dose 100 mg/day in 2-4 divided doses. Side effects are bone marrow suppression, proteinuria.

Drug reducing copper absorption: (a) Zinc induces metallothionien (MT) synthesis in intestinal cells and thus blocking absorption of copper. Dose – 150 mg/day. (b) Tetrathiomolybdate (TM) is the most effective anti-copper agent.

Diet - Avoid copper rich foods such as meat, shell fish, nuts, chocolates, cocoa, mushrooms.

Liver transplantation - If fulminant hepatic failure, decompensated hepatic disease with encephalopathy, coagulopathy, refractory portal hypertension.

Short term measures include haemodialysis and plasma exchange and are indicated in severely ill patients who cannot wait for 2–6 months for action of copper removing agents to become effective.

Maintenance therapy. Zinc 150 mg/day drug of choice. Alternatively penicillamine plus trientine, but these drugs are toxic and should not be used in those who are asymptomatic.

Chorea

(a) **Sydenham's chorea** (Chorea minor) – One of the neurological manifestations of acute rheumatic fever. Associated credits and arthritis may be presents. Head and upper limbs are predominantly involved.

(b) **Huntington's chorea** (Chronic progressive chorea) – A hereditary disorder starting in early middle age and characterised pathologically by degeneration of ganglion cells of forebrain and corpus striatum and clinically by choreiform movements and progressive dementia. The rigid form may simulate Parkinsonism (Table 65).

Treatment – Phenothiazine derivatives, e.g. pimozide may be helpful in reducing aggression and hyperactivity as well as in controlling movements. *Reserpine derivatives* such as tetrabenzene, can be effective in controlling movements, but may aggravate depressive tendencies. GABA receptor antagonist, e.g. baclofen may be useful in combination with other therapy.

Table 65: Differences between Parkinson's disease and Huntington's chorea

	Parkinson's disease	*Huntington's chorea*
Site of neuronal loss	Substantia nigra	Caudate nucleus
Neurotransmitter loss	Dopamine	Acetylcholine (and GABA)
Excess of	Acetylcholine	Dopamine
Levodopa therapy	Improvement	Exacerbation of chorea
Phenothiazine	Exacerbation	Improvement of chorea

(c) *Senile chorea* – Choreiform movements following vascular lesions of brain in middle or old age. Usually of sudden onset and unilateral.

(d) *Chorea associated with systemic disease* – SLE, polycythemia rubra vera, thyrotoxicosis, encephalitis lethargica, acanthocytosis, hypocalcemia, hypernatremia.

(e) *Drug-induced chorea* – Neuroleptics, phenytoin, amphetamines, levodopa, oral contraceptive pill.

(f) *Hereditary non-progressive chorea.*

Multiple System Atrophy (MSA)

Three overlapping degenerative conditions:

(a) *Progressive autonomic failure* – (Shy-Drager syndrome) – Impotence and incontinence early symptoms. Later autonomic disturbance with postural hypotension, failure of sweating and respiratory problems including sleep apnoea.

(b) *Olivopontocerebellar degeneration* – Progressive cerebellar, limb and gait ataxia with dysarthria and nystagmus. Presence of pyramidal signs.

Urinary and orthostatic symptoms in a Parkinsonian pt. within one year history of motor symptoms suggests a diagnosis of NSA-P and their absence suggests PD.

(c) *Striatonigral degeneration* – Akinetic syndrome most likely to be confused with Parkinsonism.

Progressive Supranuclear Palsy (Table 66)

Cerebral Anoxia

Diffuse cerebral anoxia resulting usually from cardiorespiratory arrest can lead to Parkinsonism due to bilateral basal ganglia infarction. In younger people severe hypotension with hypoxia in opiate overdosage and carbon monoxide poisoning are the usual causes.

Dystonia Musculorum Deformans (Torsion Spasm)

Disease of basal ganglia of unknown aetiology characterised by occurrence of slow, strong, sustained, twisting, turning and writhing movements of the somatic muscles, particularly muscles of girdle and trunk. Abnormal movements and spasm of muscles produce bizarre stepping gait and often dysarthria, facial grimacing and torticollis.

Table 66: Comparison between idiopathic Parkinson disease and progressive supranuclear palsy

Features	*Idiopathic Parkinsonism*	*Progressive supranuclear palsy*
Rigidity	Present	Present
Bradykinesia	Present	Present
Tremors	Universal	Rare
Asymmetric findings	Common	Rare
Ocular problems	Uncontrolled blinking Excessive watering of eye Diplopia	Vertical gaze palsy (Supranuclear) Eyelid apraxia, Blepharospasm (Lid freezing)
Posture	Tend to fall forwards as, if chasing centre of gravity	Tend to fall backwards due to head tilt backwards
Pseudobulbar features	Absent	Common
Cognitive deficits	Common in advanced disease	Noted in virtually all patients
Dysautonomia	Infrequent	Infrequent
Pathology	α-Synucleinopathy	Tauopathy
MRI brain	Not required with typical presentations Useful to rule out other disorders like normal pressure hydrocephalus, mass lesions and vascular disease	Midbrain atrophy "hummingbird sign"

Spasmodic Torticollis

Usually starts in adolescence or early adult life and characterized by marked tonic or clonic movements of sternomastoid, trapezius and other muscles of neck. This results in the neck being twisted to one side, the shoulder being elevated and sometimes the head tilted backwards. The movements are intermittent, aggravated by emotion and anxiety and stop during sleep. Distinction between hysterical and organic torticollis may be difficult.

20. HEREDITARY AND DEGENERATIVE DISORDERS

CEREBRAL PALSY

The term cerebral palsy refers to a variety of neurological deficits, permanent but nonprogressive, mainly affecting motor function, as a result of prenatal insult, birth injury or some illness in early infancy. In addition to motor defects, intellectual impairment is common.

Risk Factors

Prenatal – Malformations, obstructive lesions in the brain (e.g. cysts, periventricular leucomalacia), infection, exposure to toxins, genetic predisposition. *Perinatal* – Asphyxia, hemorrhage, low birth weight, prematurity, kernicterus. *Postnatal* – CNS infection and trauma.

Clinical Features

1. Spastic:
   (a) *Spastic hemiplegia* – Commonest type. May be associated hemisensory and hemianopic visual field defect, and sometimes dysphasia. Seizures may occur.
   (b) *Spastic diplegia* – Difficulty in walking, scissor gait. Upper limbs relatively spared. Lower limbs affected more.
   (c) *Tetraplegia* – Equal involvement of all four limbs. Seizures likely, and primitive reflexes (tonic neck, Moro, sucking, grasping) persist well-beyond normal age. Limbs may become spastic by end of first year.
2. Extrapyramidal – Choreoathetosis and dystonia. Associated difficulty in articulation, drooling and emotional lability. Usually normal intelligence.
3. Ataxic – Cerebellar ataxia often associated with mental retardation.
4. Mixed syndrome – Combination of spastic paraplegia and ataxia.

Investigations

(a) Chromosome analysis, if features are dysmorphic or intrauterine growth is poor. (b) EEG, if seizures. (c) Brain imaging to look for maldevelopment, atrophy, periventricular leucomalacia, or migration defects.

Management

1. *Physiotherapy* – to be started early.
2. *Drugs* – (a) Spasticity – Baclofen acts peripherally, dantrolene has direct effect on muscle. (b) Dystonia – Diazepam, benzhexol, tetrabenzene.
3. *Surgery* – (a) Neurosurgical – Selective dorsal root rhizotomy. (b) Orthopaedic for contractures and other deformities.

SYRINGOMYELIA

A chronic progressive disorder in which cavitation (syrinx = pipe) develops within the spinal cord, either involving the central canal, the central grey matter of the spinal cord usually cervical and sometimes extends into the lower brainstem (syringobulbia).

Pathological Classification of Syringomyelia

Type I: With obstruction of foramen magnum and dilatation of central canal:

(a) With type I Chiari malformation.

(b) With other obstructive lesions of foramen magnum.

Type II: Without obstruction of foramen magnum (idiopathic).

Type III: With associated disease of spinal cord – Tumours, arachnoiditis, traumatic myelopathy.

Type IV: Pure hydromyelia with or without hydrocephalus.

Aetiology – (a) Usual age 25–40 years, more common in males. (b) Common segment affected first is 1st thoracic. (c) Associated conditions. (i) Congenital – Frequent association with Arnold-Chiari malformations. (ii) Acquired – Spinal cord tumors, basal arachnoiditis, late sequel of trauma.

Mechanism – (a) Hyperdynamic theory – Intermittent obstruction of CSF outflow from fourth ventricle increases pressure within the dilated central canal (hydromyelia) which ruptures into the substance of the cord to form a syrinx (syringomyelia). (b) In acquired type, syringomyelia probably follows intramedullary necrosis and reabsorption.

Clinical Features

1. *Onset* – (a) Wasting and weakness of small muscles of hands. (b) Loss of sensations, pain, or trophic lesions over trunk and upper extremity.
2. *Sensory symptoms* – Dissociated sensory loss, usually first on one side. Cranial extension of the syrinx cuts the trigeminal fibres, producing a typical Balaclava helmet sensory disturbance with preservation of sensation around eyes, nose and mouth.
3. *Motor symptoms* – Wasting of small muscles of hands, contractures. Leg involvement with spastic paraparesis is more insidious. Cervical lesions from C_5 upwards may produce coarse, rotating nystagmus, vertigo, Horner's syndrome and ataxia.
4. *Trophic* – Thickening of subcutaneous tissues, 'sausage fingers', Charcot's joints, ulcers, and necrosis of bones.
5. *Syringobulbia* – Earliest signs are onion-skin sensory loss over outer part of face (due to involvement of lower part of 5th nerve nucleus), dysphagia and dysphonia.
6. *Associated abnormalities* – Kyphoscoliosis, cervical rib, spina bifida, pes cavus. Associated Arnold-Chiari malformation may produce brainstem and cerebellar signs and symptoms.

7. *Bladder involvement* is late in syringomyelia.

Investigations

MRI demonstrates syrinxes clearly (Figs. 60 and 61).

Management

Surgical decompression of craniovertebral junction can often prevent further deterioration and may be combined with insertion of a syringoperitoneal shunt to prevent development of secondary hydrocephalus.

ANTERIOR HORN CELL DISEASES

1. Inherited:
   - *Infantile progressive muscular atrophy* (Werdnig-Hoffman disease) – Usually begins at birth or before 6 months of age. Genetically determined. Infant limp and floppy. Prognosis poor, death usually within first year.
   - *Juvenile familial benign muscular atrophy* – Usually seen later in infancy. Differs from Duchenne type of dystrophy by presence of muscle fasciculation, denervation atrophy on EMG, and normal serum creatine kinase.
   - *Juvenile muscular atrophy* (Kugelberg- Welander disease) is like infantile progressive muscular atrophy autosomal recessive disorder of lower motor neurones. It begins between 2 and 17 years of age, with a slower evolution and longer life expectancy. Walking may still be possible in middle age. Although simulating muscular dystrophy, it may be differentiated by EMG and muscle biopsy which reveal presence of neurogenic atrophy.
   - *Progressive muscular atrophy.*
2. Infective – Anterior poliomyelitis.

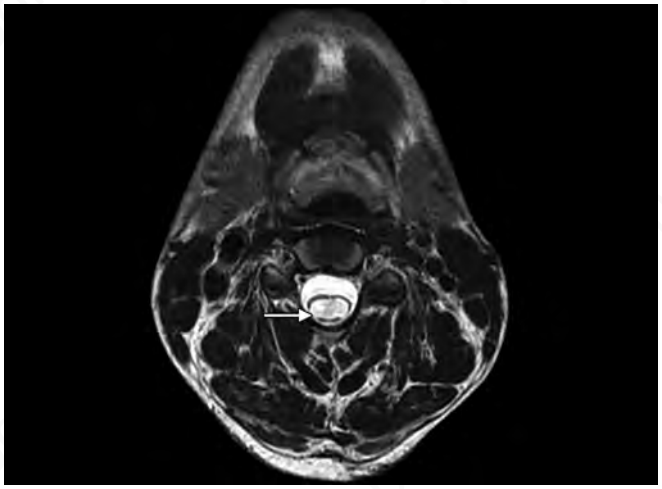


Fig. 60: MRI axial T2 image showing syrinx

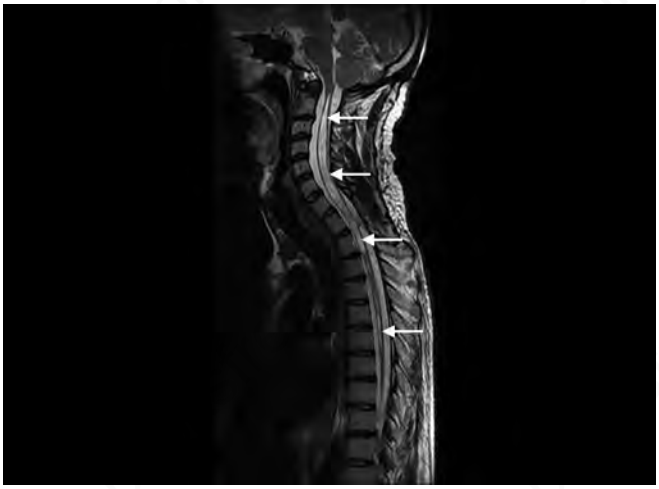


Fig. 61: MRI T2 image showing syrinx in cervico-dorsal region

3. Toxic – Triorthocresyl phosphate poisoning. Tick paralysis.
4. Electric shock.

MOTOR NEURON DISEASE (MND)

MND is a progressive neurodegenerative disease. In the classical form (also termed 'amyotrophic lateral sclerosis') degeneration of corticospinal tract neurons in the motor cortex (upper motor neurons) and brainstem and spinal cord motor neurons (lower motor neurons) results in a unique combination of upper and lower motor neuron signs. The male: female ratio is 1.5:1. In sporadic MND, mean age of onset is 60 years, in the familial form about 50 years. Table 67 for variour types of motor neuron disease.

Table 67: Clinical patterns of MND

Amyotrophic lateral sclerosis
Progressive muscular atrophy (PMA)
Progressive bulbar paralysis
Primary lateral sclerosis
Others
1. *Familial MND* – Chromosome 21.
2. Variants of MND
• Madras MND. Young adult, slowly progressive asymmetrical wasting and weakness of limbs along with pyramidal involvement, resulting ultimately in features of ALS. Raised serum pyruvate levels.
• Monomelic amyotrophy. Adolescents. Progressive weakness and wasting of one limb (usually upper) commonly wasted muscles are elbow flexors followed by small hand muscles.
• Hemiplegic MND
• Wasted leg syndrome
• Crural ALS
• MND with Parkinsonism
• MND with dementia

Amyotrophic Lateral Sclerosis

Clinical Features

History – 5–10% of patients with MND have a family history, suggesting an autosomal dominant trait; 20% of such families have mutations of the Cu, Zn superoxide dismutase (SOD 1) gene on chromosome 21.

Limb weakness – Majority of patients present with progressive asymmetrical weakness of the limbs. This begins in the leg as foot drop, in the hands with difficulty of fine movements. Localized wasting is common, and fasciculations are often present. Severe cramps may precede weakness.

Bulbar symptoms – are the presenting feature in about 25% of patients. Dysarthria is either in the form of nasal speech (bulbar palsy) or, more commonly, spastic dysarthria (pseudobulbar palsy), or a combination of two. This is followed by dysphagia with drooling of saliva.

Other presentations – A small number presents with respiratory failure. Involvement of bladder and bowels is uncommon. Dementia of frontal lobe type may be seen in about 2%.

Examination

- Muscular fasciculations
- Weakness

- Wasting
- Brisk tendon reflexes
- Extensor plantars
- Brisk jaw jerk (bulbar onset)
- Spasticity (marked in younger patients)
- Eye movements normal
- Dysarthria (involvement of bulbar muscles)
- Reduced cough and gag reflex
- Tongue shows wasting and fasciculations
- Normal sensation
- No bladder or bowel disturbance
- Tachypnoea due to ventilatory failure

Progressive Muscular Atrophy (PMA)

Most benign variety of motor neuron disease. (Pure LMN presentation).

(a) Atrophy, weakness and fasciculations. Onset usually with wasting of one hand (first dorsal interosseous muscle). Tendons become prominent as hand muscles waste, giving guttered appearance (Skeleton hand). Eventually wasting spreads to all four limbs and trunk. (b) Loss of tendon reflexes.

Progressive Bulbar Paralysis

- Dysphagia followed by dysarthria.
- Nasal regurgitation of fluids and nasal slurred voice.
- Tongue wasted and folded and fasciculations visible.
- Absent jaw jerk and gag reflex.
- Rapid progression.

Primary Lateral Sclerosis

Refers to slowly progressive spasticity and weakness of the limbs, more marked in the legs, which may be associated with pseudobulbar palsy. It has a better prognosis (Pure UMN presentation).

Pseudobulbar Palsy

Degeneration of corticobulbar pathways of V, VII, IX, XI and XII cranial nerve nuclei.

- Weakness of muscles of mastication and difficulty in chewing.
- Expressionless face
- Exaggerated jaw jerk. Brisk gag reflex
- Palatal weakness allowing food and fluid to enter nasopharynx
- Monotonous speech
- Tongue immobile and cannot be protruded
- Emotional lability – Spontaneous outbursts of laughing and crying.

Investigations

No specific test. Investigations are performed to exclude other conditions – (a) *MRI of spinal cord* – to exclude compressive lesion in neck. Cranial MRI in patients with bulbar onset to exclude brainstem lesions. On T_2-weighted images, high intensity lesions are visible in motor cortex, internal capsule and brainstem. (b) *EMG and nerve conduction studies* – reveal anterior horn cell damage but do not specify the cause. (c) Creatine phosphokinase may be slightly raised. (d) CSF is normal.

Management

MND progresses rapidly and is hence difficult to manage.

Drug treatment – (a) Riluzole, a glutamate release inhibitor used early in the evolution of the disease may prolong survival. (b) Botulinum toxin to control drooling. (c) Baclofen or Tizanidine for spasticity. (d) Antidepressant drugs. (e) Gastrostomy to reduce expiration.

Symptomatic Treatment

Depression and insomnia – Antidepressants.

Dysphagia – Food thickeners initially, but definitive procedure is percutaneous endoscopic gastrostomy.

Dysarthria – Speech and language therapy.

Ventilatory failure – Non-invasive nocturnal nasal intermittent positive pressure ventilation in some patients who have good bulbar and limb function.

Spasticity – Baclofen or dantrolene. Quinine for muscle cramps.

Dyspepsia – Antacids, H_2-blockers or omeprazole.

Excess saliva – Anticholinergics such as benzhexol or antidepressant, e.g. amitriptyline, dothiepin. Radiotherapy to parotid gland if these measures fail.

Related Disorders

1. Kennedy's syndrome (Bulbar and spinal muscular atrophy) – X-linked LMN disease. A rare form of MND with near normal life expectancy. Presents in males between ages of 20 and 50. Features: Mild dysarthria, wasted fasciculating tongue, tremor, proximal weakness with wasting and fasciculations, Gynecomastia and reduced fertility.
2. Multifocal motor neuropathy (MMN) – occurs in men under 45, with asymmetrical, progressive, mainly distal weakness with onset in the arms. Signs include fasciculations, wasting and reduced reflexes. EMG shows multifocal conduction block. High serum titres of antibodies to GM_1 ganglioside often detectable. May respond to treatment with i.v. human immunoglobulin, plasmapheresis or cyclophosphamide.

3. Spinal muscular atrophy (SMA) – Diseases that usually present in infancy or childhood and affect only lower motor neurons.
   - *Type I SMA* (Werdnig-Hoffman disease) presents at birth with hypotonia, reduced movements, proximal weakness, wasting and reduced reflexes. Death before one year of age.
   - *Type II SMA* presents at about 6 months, and has a more protracted course. Death from respiratory failure before age of 10.
   - *Type III SMA* (Kugelberg-Welander disease) presents at about 10 years with life expectancy of about 35 years. Progression tends to be slower than lower motor neuron forms of MND.
   - *Type IV SMA* has an early adult onset. Survival may be normal.

Differential Diagnosis

Table 68 for the differential diagnosis of MND.

Madras MND - Young adults, slowly progressive asymmetrical wasting and weakness of limbs along with pyramidal involvement, resulting ultimately in features of ALS. Raised serum pyruvate levels.

Table 68: Differential diagnosis of MND

Disorder/syndrome	*Main diagnostic test*
Cerebral and brain disorders	
• Infiltrating tumors	• Cranial MRI
• Vascular disorders	• Cranial MRI, CSF, ESR, C-reactive protein, autoantibodies (e.g. multifocal infarction, vasculitis, A- V malformations)
• Syringobulbia	• Cranial MRI
• Cranial neuropathies	• CSF, ESR, CRP, autoantibodies, EMG
• Creutzfeldt-Jakob disease	• EEG, prion gene analysis
Spinal cord disorders	
• Cervical radiculomyelopathy	• Cervical MRI, CT, myelography
• Cervical myelopathy with lumbosacral radiculopathy	• EMG studies, MRI
• Syringomyelia	• MRI
• Intramedullary tumours	• MRI
• Infiltrations (e.g. Ca, lymphoma)	• MRI, CSF analysis
• Infections (e.g. syphilis)	• Serological tests for syphilis.
• HIV-associated syndromes	• HIV antibodies
• HTLV-1-associated myelopathy	• HTLV-1 antibodies

Contd...

SPINOCEREBELLAR DEGENERATIONS

1. Friedreich's ataxia – (Refer)
2. Familial spastic paraplegia – Family history of pure motor paraparesis in siblings or parents. Usually patient presents in the first decade. Pes cavus is often present.
3. Abetalipoproteinaemia – If untreated may produce similar neurological picture.
4. Due to unknown biochemical abnormality – Hereditary spastic ataxia (Marie), hereditary areflexic dystasia (Roussy-Levy), and olivopontocerebellar atrophy.

21. CEREBELLUM AND ITS DISORDERS

ANATOMY

The cerebellum. Situated in the posterior fossa beneath the tentorium, and attached to the brainstem by the superior, middle and inferior peduncles, comprises two lateral hemispheres and the vermis which contains afferent and efferent nerve fibres.

Afferent Connections

Functionally, the cerebellar cortex is divided into three parts:

Contd...

Disorder/syndrome	*Main diagnostic test*
• Vasculitis	• ESR, CRP, autoantibodies
• Spinal A-V malformations	• MRI, myelography, spinal angiography
Heredofamilial disorders mimicking MND	
• Kennedy's syndrome	• EMG, androgen receptor mutation
• Late-onset spinal muscular atrophy	• EMG, gene mutation analysis
• Hexosaminidase A, B deficiency	• Enzyme analysis
Metabolic and toxic disorders	
• Thyrotoxicosis	• TSH, T4
• Hyperparathyroidism	• PTH, calcium
• Lead poisoning	• Lead levels in serum
Neuromuscular disorders that may mimic MND	
• Myasthenia gravis	• Edrophonium test, acetylcholine receptor antibody, RNS
• Lambert-Eaton syndrome	• EMG, calcium channel antibodies, RNS
• Myopathy (e.g. inclusion body myositis, scapuloperoneal dystrophy)	• EMG, muscle biopsy
• Multifocal motor neuropathy	• EMG, nerve conduction studies – conduction block

1. *Vestibulocerebellum* – (lower vermis), which receives afferents from the vestibular system.
2. *Spinocerebellum* – (upper vermis and anterior parts of the hemisphere), which receives afferents from the spinal cord.
3. *Neocerebellum* – (cerebellar hemispheres), which receive afferents from the cerebral cortex.

Efferent connections: Efferent fibres originate from the Purkinje cells and pass to either the vestibular nuclei or deep cerebellar nuclei, which gives rise to a variety of ascending and descending projections. Each cerebellar subdivision sends efferents principally to that part of the nervous system from which it receives its afferents.

Afferent connections (Table 69).

Table 70 gives conditions causing cerebellar dysfunction

CLINICAL FEATURES: OF CEREBELLAR LESION

A. Localizing value

I. Disorders of postural fixation:
   1. *Hypotonia.*
   2. *No rebound* – on displacing the out stretched arm.
   3. *Pendular knee jerk.*

II. Disorders of movements:
   1. *Intention tremor* – Increased irregularity of movement as the finger approaches the nose in finger-nose test.
   2. *Dysmetria* – Inability to arrest movement at desired point, e.g. exaggerated splaying of fingers in grasping a small object, or lifting the leg too high when attempting to place it on a chair with eyes shut.
   3. *Dyssynergia* – Defective co-ordination of various muscles and muscle groups participating in a movement, e.g. extending the trunk backwards without simultaneous flexion of the knees thus losing balance.
   4. *Dysdiadochokinesia* – Disturbance of rapid alternating movements, e.g. rapid pronation and supination of forearm, or tapping the thigh alternately with the palm and the back of the hand.
   5. *Scanning speech.*
   6. *Head tilt* – suggests lesion of inferior vermis. (Trochlear nerve palsy and tonsillar herniation can also produce such abnormal posture).

III. Disorders of gait:
   1. Broad based and reeling gait.
   2. Deviation to side of lesion.
   3. Truncal ataxia (unsteadiness when seated). Spinocerebellar ataxia (SCA).

Table 69: Afferent cerebellar connections

Cerebellar cortex	*Afferent connection*	*Dysfunction*
Vestibulocerebellum (lower vermis)	Vestibular system	Truncal ataxia
Spinocerebellum	From spinal cord	Unsteadiness of gait and stance (positive Rombergism)
Neocerebellum	From cerebral cortex	Ataxia of intended limb movements (past-pointing, intention tremor)

B. Non-localizing

1. Static tremors due to hypotonia.
2. Eye movements – (a) Nystagmus –In unilateral disease, amplitude and rate increase when looking towards diseased side. (b) Skew deviation. (c) Ocular dysmetria – An 'overshoot' when the eyes voluntarily fixate.

Table 70: Causes of cerebellar dysfunction

I. **Acute:**
   1. *Infection* – Encephalitis, abscess, Guillain Barre variant.
   2. *Vascular* – Syndrome of posterior inferior cerebellar artery, anterior inferior cerebellar artery or superior cerebellar artery. Vertebrobasilar insufficiency.
   3. *Demyelinating* – Multiple sclerosis.
   4. *Drugs* – Phenytoin, barbiturates, streptomycin, gentamicin, kanamycin, piperazine citrate.
   5. *Toxic* – Alcohol.
   6. *Hyperpyrexia.*

II. **Chronic:**
   1. *Developmental* – Agenesis, craniovertebral anomaly, Dandy Walker syndrome, von Hippel Lindau disease.
   2. *Familial* – e.g. Refsum's disease, lipidoses, leucodystrophies.
   3. *Degenerative* – Primary cerebellar degeneration, olivopontocerebellar degeneration, olivorubrocerebellar degeneration, delayed cerebellar degeneration. Spinal cerebellar ataxia (SCA).
   4. *Neoplastic* – CP angle tumour, pontine tumour, cerebellar tumour.
   5. *Metabolic* – Alcohol, myxoedema, inborn errors of metabolism, non-metastatic manifestation of malignancy.

3. Disturbance of speech – Scanning dysarthria with speech occasionally delivered with sudden force – explosive staccato speech.
4. Vertigo – Objects move away from the side of lesion. Sense of rotation of the body in same direction with intra-cerebellar lesion, in opposite direction with extra-cerebellar lesion.
5. Titubation – Rhythmic nodding tremor of head from side to side or to and fro usually associated with distal limb tremor.
6. Pendular knee jerk.

INVESTIGATIONS

First-line

1. CT and MRI – will usually differentiate between cerebellar tumours, cerebellar stroke and other forms of cerebellar disease such as degeneration and demyelination.
2. Presence of antineural antibodies, MRI, CSF (paraneoplastic, neurologic disorders).
3. Thyroid function tests
4. Vitamin E
5. α-fetoprotein
6. Lipid profile
7. Investigations for malignancy (CXR, abdominal ultrasound)
8. Visual evoked response

Second-line

1. CSF – to detect cerebellar inflammation
2. Antineuronal antibodies (Paraneoplastic)
3. EMG – for neuropathy
4. SCA mutations, mitochondrial gene analysis
5. DRPLA mutation – if family history
6. Fundal examination – Angiomas in cerebellar angioblastoma.

DIFFERENTIAL DIAGNOSIS

Ataxia is clumsiness of movement in absence of motor and sensory deficit.

1. Cerebellar tumours – Ataxia, symptoms of increased intracranial pressure (caused by hydrocephalus due to obstruction of fourth ventricle). Astrocytomas and medulloblastomas occur almost exclusively in children.
2. Cerebellar stroke – (a) *Infarction* – Patients present with vertigo, headache, vomiting and ataxia. May have signs of brainstem involvement including ipsilateral Horner's syndrome, contralateral hemisensory loss and cranial nerve involvement. (b) *Hemorrhage* – Symptoms are difficult to differentiate from infarction. Hypertension and anticoagulation are risk factors.
3. Inflammatory disease of cerebellum

   (a) *Multiple sclerosis*. (b) *Brain abscess* secondary to disease in the ear and mastoid cells. (c) *Cerebellar encephalitis* – from viral infection, e.g. varicella, less often measles, mumps and rubella. Onset of cerebellar syndrome days or weeks after infection.
4. Degenerative and symptomatic ataxias

   (a) *Friedreich's ataxia* – (Refer)

   (b) *Ataxia-telangiectasia* – starts in early childhood. Combination of neurological symptoms (ataxia, choreoathetosis, defective horizontal conjugate gaze), cutaneous and conjunctival telangiectasias, immunological abnormalities which predispose to recurrent infections and increased incidence of malignancies. Increased levels of serum α-fetoprotein.

   (c) *Multiple system atrophy* – (Refer)

   (d) *Episodic ataxias* – Autosomal dominant inherited disorders which differ from other types of ADCAs by the intermittent nature of the ataxia, which may last from minutes to a few days. Frequency of attacks is reduced by acetazolamide.

   (e) *Idiopathic cerebellar ataxia* (IDCA) – A sporadically occurring disorder of unknown cause characterised by progressive ataxia. Onset usually at age of 50-60 years. Additional extra-cerebellar symptoms (parkinsonism, autonomic failure, spasticity, bulbar symptoms). Olivopontocerebellar atrophy is the pathological lesion.

   (f) *Spinocerebellar ataxia* – (SCA) – Autosomal dominant. Progressive cerebellar syndrome with ataxia of stance and gait of limb movements, dysarthria and oculomotor abnormalities such as gaze paresis. Also corticospinal tract signs – spasticity, extensor plantars, diminished vibration sense, dysphagia.

   (g) *Abetalipoproteinaemia or toxins* – anti-epileptic drugs, lithium, cyclosporine.

(h) *Immune-mediated:*
- Multiple sclerosis
- Miller Fisher syndrome
- SLE
- Paraneoplastic (small cell lung ca, breast or ovary.

(i) *Symptomatic ataxia* – Sporadically occurring ataxias due to toxic, endocrinological, paraneoplastic, nutritional or infectious causes. (i) *Ataxia due to alcoholism* – Ataxic gait, postural tremor. No major involvement of the upper extremities. Pathological changes comprise loss of Purkinje cells of vermis and anterior parts of cerebellar hemispheres resulting in a typical pattern of atrophy in imaging studies. (ii) Due to – Antidepressants, antiepileptic drugs lithium, cyclosporine, metronidazole. (iii) *Paraneoplastic cerebellar ataxia* – An uncommon manifestation of cancer, usually associated with ovarian, breast or small cell lung cancer or Hodgkin's disease. Patients present with subacute onset of a cerebellar syndrome, with severe ataxia, oculomotor abnormalities and dysarthria. The presence of auto-antibodies recognizing neural antigen suggests an immune-mediated disorder.

(j) *Spinocerebellar ataxia* (Table 71).

22. MYOPATHIES

The term myopathy may be used to define any disease in which the patient's symptoms and/or physical signs can be attributed to pathological, biochemical or electrical changes which are occurring in the muscle fibres or in the interstitial tissues of the voluntary musculature, and in which there is no evidence that the symptoms related to the muscles are in any way secondary to disordered function of the central or peripheral nervous system.

Table 71: Distinguishing features of cerebellar and sensory ataxia

	Cerebellar ataxia	*Sensory ataxia*
Muscle power	Normal	May be reduced
Deep reflexes	Pendular	Absent
Post. column signs	Absent	Present
Neuropathic features	Absent	May be present
Romberg's sign	Negative	Positive
Gait	Broad based	Stamping

Muscle disorders may be genetically determined or may result from autoimmune disorders, systemic diseases or the effects of a variety of exogenous toxins. They can be classified in terms of causative genetic mutations, by specific protein deficiencies, on the basis of histopathological changes, by pathogenic mechanisms, and by clinical phenotype.

GENETICALLY DETERMINED MYOPATHIES

There are four main groups of genetic myopathies:

1. ***Muscular dystrophies*** are due to abnormal muscle protein and generally characterized by fibre necrosis and replacement of muscle by fat and fibrous connective tissue. Different types of muscular dystrophy can be recognised by clinical features (e.g. muscle hypertrophy, contractures, evidence of cardiac involvement, and by the pattern of involvement of muscle groups). Three main pattern are – axial and limb girdle weakness, non-limb girdle weakness pattern with prominent involvement of cranial musculature, and distal weakness.
2. ***Congenital myopathies*** are classified by specific histological and ultrastructural features.
3. ***Myotonias and periodic paralyses*** are associated with disturbance of muscle ion channels (muscle channelopathies).
4. ***Genetically determined metabolic myopathies*** include disorders of glycogen and lipid metabolism, malignant hyperthermia and mitochondrial cytopathies.

Muscular dystrophies – with predominantly axial and limb girdle weakness.

Pseudo-hypertrophic muscular dystrophy – [Duchenne muscular dystrophy (DMD)].

Aetiology – Age – 5 to 10 years, rare after puberty. Sex – X-linked recessive disease is confined to males, though occasionally seen in females with Turner's syndrome. Familial – exhibited by males but transmitted by females.

Clinical Features

1. *Onset* – gradual, clumsiness and frequent falls.
2. *Attitude on standing* – Marked lordosis of lumbar spine, shoulders held far back and scapulae project. The large size of the buttocks makes the lordosis appear more accentuated than it is in reality. Abdomen protuberant.
3. *Muscles* – Usually involved symmetrically: (i) Hypertrophy of – deltoid, infra-spinal, glutei, quadriceps and calf muscles; less often supraspinati, triceps and biceps; rarely serratus anterior, muscles of forearms and masseters. Macroglossia is sometimes observed. (ii) Atrophy of – lower portion of pectoralis major,

biceps, latissimus dorsi and thigh muscles. (iii) Muscles not affected – hands and face. The weakness of the shoulder girdle muscles is easily demonstrated by picking the child up under his arms, when the arms go up and the child tends to slip through one's hands.

4. *Gait* – When walking the child waddles. The trunk and head are usually held very erect. In sitting, the lordosis, which is present on sitting passes into a kyphosis, the back being bent according to the degree of weakness of the dorsal muscles.
5. *Rising from the ground* (Gower's sign) – The child attempts to rise by 'walking up his legs'. This manoeuvre may be considered pathognomonic of the disease.
6. *Cardiomyopathy* – seen in almost all patients. Congestive heart failure seldom occurs except with severe stress such as pneumonia. Cardiac arrhythmias are rare. The typical electrocardiogram (ECG) shows an increased net RS in lead V1; deep, narrow Q waves in the precordial leads; and tall right precordial R waves in V1.
7. *Intellectual impairment* -in Duchenne dystrophy is common

Progress – Death usually occurs between ages of 18–22 years from respiratory infection and/ or cardiac failure.

Becker muscular dystrophy – Age of onset 3 to 20 years, similar clinical picture as DMD, but clinical course much more benign. Myocardial and intellectual impairment is much less common. Exertional myalgia is a common presenting symptom. Calf muscle enlargement is often striking. Death occurs between 30–60 years of age.

Pathogenesis – BMD and DMD are forms of dystrophinopathy. Dystrophin, a component of the cytoskeleton lying beneath the muscle fibre, is one of the largest proteins in the body. Dystrophin deficiency results in loss of structural integrity of the muscle surface membrane. Mutations of the encoding gene may be 'out of frame' resulting in complete absence of dystrophin, causing DMD, or 'in frame' producing partial dystrophin deficiency characteristic of BMD.

Diagnosis of dystrophinopathy may be suggested by the history and physical signs, with very high serum creatinine kinase (CK), and can usually be confirmed by standard DNA analysis which detect the common dystrophin gene deletions in 70% of patients. Most patients require muscle biopsy.

Management – Prednisolone 0.5–1.5 mg/day has been shown to improve natural history of DMD for up to 2 years. Gene therapy, using myoblasts and other cells transfected with the dystrophin mini-gene may restore muscle dystrophin. Otherwise physical therapy, use of orthoses and surgical correction of spinal and other deformities.

Muscular dystrophy in females – DMD and BMD have occasionally been reported in females in patients with Turner's syndrome. In about 65% of cases, the mothers are carriers of the gene. A proportion of adult females with limb-girdle myopathies will be 'manifesting' carriers of either DMD or BMD.

Limb-girdle muscular dystrophies (LGMDs) – LGMDs are a complex, genetically heterogenous group of disorders, but can be divided into two broad clinical groups:

Milder forms usually present between 20–30 years of age, with progressive difficulty in walking followed by proximal arm weakness and loss of ambulation after 20–30 years; however age of onset and progression vary. Neck and shoulder muscles become weak. Muscles of shoulder and pelvic girdles, and proximal arm and leg muscles become weak and wasted. Distal involvement and calf hypertrophy is variable. Bilateral scapular winging is typical and often early feature.

Severe forms present in childhood. Severe childhood autosomal recessive muscular dystrophy (SCARMD) is clinically similar to DMD and is the most common cause of a DMD-like phenotype in girls. However cardiac and mental function are unaffected.

CK levels are increased by tenfold to more than 100-fold. Biopsy findings may range from mild, nonspecific dystrophic changes in milder forms to severe, often very focal fibre necrosis in SCARMD.

Emery-Dreifuss muscular dystrophy (EDMD) presents in childhood with progressive weakness and wasting of the scapulohumeral and anterior tibial and peroneal muscle groups. It accounts for most forms of 'scapuloperoneal muscular dystrophy'. Muscle contractures develop at an early stage, leading to pathognomonic posture, elbow flexion, equinovarus ankle deformities and fixed neck flexion. Cardiac involvement leads to serious conduction disorders and sometimes sudden death.

Bethlem myopathy is a relatively benign, autosomal dominant condition that progresses insidiously from infancy, causing increasing difficulty with running, then walking and standing. Significant disability develops in old age. Characteristic contractures of the fingers but not thumbs ('prayer sign') are diagnostic and associated with contractures of the elbows and equinovarus ankle deformities. The disease is caused by a deficiency of type IV collagen in the extracellular matrix of muscle fibres.

Congenital muscular dystrophies – One of the causes of 'the floppy infant'. Myopathy manifests at birth or early life. Small, weak, hypotonic muscles, proximal usually more affected than distal. Both sexes.

NON-LIMB-GIRDLE PATTERN MUSCULAR DYSTROPHIES WITH INVOLVEMENT OF CRANIAL MUSCULATURE

Facioscapulohumeral muscular dystrophy – AD transmission. Either sex. Onset usually in adolescence. Initial involvement, sometimes symmetrical, of facial and shoulder-girdle muscles, soon followed by weakness of anterior tibial and peroneal muscles, usually with spread within 20 or 30 years to pelvic muscles. Profound facial weakness produces pouting of the lips and a transverse smile. Inability to whistle is characteristic. In later stages, dramatic scapular fixators allows 'over-riding' of the scapulae above the shoulders, like a pair of wings. Foot drop and later proximal weakness can occur. Diagnostic confirmation depends on demonstration of abnormally small 4q35-specific DNA fragments following digestion with restriction site enzymes.

Oculopharyngeal muscular dystrophy presents with ptosis and weakness of extraocular muscles, muscles of the pharynx and larynx (causing progressive dysphagia and dysphonia), and facial, limb-girdle and even distal muscles. Cases may be mild to severe and present typically in the sixth decade.

Muscle biopsy can show changes which may include rimmed vacuoles and ragged red fibres typical of mitochondrial myopathy.

Distal myopathies

Several neuromuscular diseases present with distal weakness and wasting of the limbs.

Welander's, Udd's and Markesbery-Griggs type distal myopathies are all late-onset, dominantly inherited disorders of distal limb muscles, usually beginning after age 40 years.

Laing's distal myopathy is also a dominantly inherited disorder heralded by tibial weakness;it is distinguished by onset in childhood or early adult life.

Nonaka's distal myopathy and Miyoshi's myopathy are distinguished by autosomal recessive inheritance and onset in the late teens or twenties.

Congenital myopathies are classified on basis of specific histological features. Patients can present at any time from childhood to adult life, usually with distal weakness. A long, thin face and high arched palate are common. This group of disorders includes centronuclear and myotubular myopathies, nemaline myopathy and central core disease.

Myotonic disorders – Myotonia is prolonged contraction of muscle, with subsequent slowed relaxation, following activation. It results from genetic or acquired changes in excitability of muscle surface membranes and is found in several primary muscle diseases.

DYSTROPHIC MYOTONIAS

Myotonic dystrophy is the most common inherited muscular dystrophy in adults. The characteristic phenotype includes, in addition to grip and percussion myotonia:

- Progressive muscular weakness and wasting starting distally
- Bilateral ptosis and facial muscle weakness, temporalis and masseter muscle atrophy and weakness – "hatchet face"
- Sternomastoid wasting
- Cataracts
- Endocrinopathy, notably insulin resistance
- Cardiac conduction defects, which can lead to sudden death
- Bulbar and respiratory muscle weakness
- Dysphagia and gut dysfunction
- Frontal balding and calcifying epithelioma of Malherbe
- In severe cases, mental retardation

Other features of the disease cataracts, testicular atrophy, insulin resistance, constipation, hypersomnia and cognitive defects.

Laboratory Features—The Diagnosis of Myotonic Dystrophy

Gene expression can vary from asymptomatic cases with no clinical signs, to severe congenital onset disease.

Proximal myotonic myopathy is clinically and genetically distinct from myotonic dystrophy but shares a number of phenotypic features. Weakness starts and is mainly confined to proximal muscles, and cramps are common.

Non-dystrophic myotonias and periodic paralyses – A number of familial muscle diseases have been shown to result from mutations of genes encoding muscle ion channels. The defects can lead to a phenotype in which myotonia is the major manifestation, as in myotonia congenita (chloride channelopathy), or to episodic weakness, as in

hyperkalaemic periodic paralysis (calcium channelopathy). Sodium channel mutations lead to a complex mixture of phenotypes in which myotonic stiffness or periodic weakness can occur under various conditions(e.g. exercise, exposure to cold). Periodic paralysis presents with episodic, profound muscular weakness, not involving breathing and with normal consciousness, with abnormal serum potassium. Hyperkalaemic periodic paralysis is associated with myotonia, the hyperkalaemic form is not.

GENETICALLY DETERMINED METABOLIC MYOPATHIES

Disorders of intermediary metabolism – Certain genetic disorders of intermediary metabolism can affect muscle particularly or exclusively.

Pompe's Disease - Three clinical forms of α glucosidase, or acid maltase, deficiency (type II glycogenosis) can be distinguished. The infantile form is the most common, with onset of symptoms in the first 3 months of life. Infants develop severe muscle weakness, cardiomegaly, hepatomegaly and respiratory insufficiency. Glycogen accumulation in motor neurons of the spinal cord and brainstem contributes to muscle weakness. Death usually occurs by 1 year of age.

McArdle's disease – is the most common form of these disorders. Deficiency of myophosphorylase results in failure of breakdown of glycogen to glucose in muscle. Severe myalgia with cramp develops soon after start of exercise, but the patient may notice easing of symptoms as exercise continues ('second-wind' phenomenon), as alternative energy sources are mobilised. The disease can be diagnosed from absent phosphorylase on muscle biochemistry.

Mitochondrial disorders – can affect muscle specifically or as part of multisystem disease, typically involving the CNS. Large deletions of mitochondrial DNA commonly underline Kearns-Sayre syndrome and chronic progressive ophthalmoplegia. Point mutations cause a variety of syndromes including mitochondrial encephalopathy, lactic acidosis and strokes (MELAS) and myoclonus, epilepsy and ragged red fibres (MERRF). Diagnosis by demonstration of:

- Increased blood plasma lactate and CSF lactate
- Inappropriately large increase in plasma lactate on exercise testing
- Typical histochemical features (e.g. ragged red fibres and cytochrome - negative fibres on muscle biopsy).

OTHER DISORDERS

Malignant hyperthermia characterized by hyperpyrexia, rhabdomyolysis and severe acidosis induced by inhaled anaesthetic agents (halothane) or muscle relaxant (succinylcholine) is relatively common and genetically heterogenous. Other manifestations include muscle rigidity, cardiac arrhythmia, hypotension and cyanosis. Complications – Pulmonary oedema, DIC, acute kidney failure, swelling of skeletal muscles (Refer Tropical disease section). Mutations at one malignant hyperthermia locus on 19q13.1 (ryanodine receptor) also determines a congenital myopathy (*central core disease*).

King syndrome – is an AR form of malignant hyperthermia associated with congenital defects such as short stature, webbed neck, kyphosis, low-set ears, antimongolid obliquity of palpebral fissures of eyes and winged scapulae.

ACQUIRED MYOPATHIES

Inflammatory Myopathies

Inflammatory myopathy can result from a variety of acute infections, including HIV, but the idiopathic forms of polymyositis and dermatomyositis are most common.

Polymyositis typically presents with symmetrical proximal weakness, often associated with myalgia and muscle tenderness. Progression may be rapid, but more indolent forms may occur, particularly in older women.

Investigations – CK is usually raised. EMG shows a mixed picture of increased insertional and spontaneous activity ('myogenic denervation') and 'myopathic' changes (rapid recruitment of small amplitude, polyphasic potentials on contraction). Muscle biopsy typically shows lymphocytic infiltration of muscle connective tissues, with fibre necrosis, degeneration and regeneration, but the process is patchy and inflammation may be inconspicuous. Demonstration of HLA class antigens on fibres by immunohistochemistry, indicative of an immune reaction, is then invaluable for diagnosis.

Dermatomyositis is essentially an immune-mediated microangiopathy affecting principally skin and muscle, though childhood dermatomyositis can include gut involvement, resulting in GI hemorrhage. Skin lesions are diagnostic – erythema affecting light-exposed areas such as the supraorbital ridges, eyelids and malar areas, chest, knuckles, knees and elbows. Skin lesions may sometimes occur without muscle weakness, but careful investigation

usually confirms muscle involvement. There is an association between dermatomyositis and underlying malignancy and this should be of consideration in men with dermatomyositis presenting over age of 55 years.

Management – Treatment begins with i.v. immunoglobulin 0.4 g/kg/day for 5 days, followed by high oral dose corticosteroids 1 mg/kg p.o., with azathioprine 1–2 mg/kg. Dose of corticosteroid should be tapered reasonably rapidly, depending on clinical response and serial CK measurements, and switched to alternate-day regimen after about one month. Use of etidronate with calcium supplements can help prevent corticosteroid-induced osteoporosis. Avascular necrosis of femoral head is a rare complication.

Inclusion body myositis – is the most common cause of acquired myopathy in those over age of 50. It has many common features with polymyositis, but tends to be indolent in progression, is not associated with myalgia and causes marked muscle wasting, particularly distally. *Muscle biopsy* is diagnostic. Up to 10% fibres show 'rimmed vacuoles' – areas of probable nuclear dissolution containing a number of aberrant proteins, including β-amyloid and hyperphosphorylated tau protein, strikingly reminiscent of changes in the brain in Alzheimer's disease. Response to immunosuppressive treatment is usually minimal and progression is inevitable.

Myopathies in systemic disease – Muscle can be involved directly as in infectious diseases, or indirectly through the effects of metabolic derangements or immune responses. Myopathy can be a feature of any endocrine disorder and can be affected by a variety of drugs.

Specific congenital myopathies – are rare disorders which present with undue floppiness in infancy – (1) *Central core disease* – is characterised by presence of one or more cores which run axially along the fibres. The disease is compatible with a normal ambulant life. Risk of developing malignant hyperpyrexia. (2) *Nemaline myopathy* – runs a benign course in childhood but may later progress. Skeletal abnormalities such as scoliosis, high arched palate, arachnodactyly.

METABOLIC MYOPATHIES

Clinical Patterns

1. ***Infantile hypotonia*** (Floppy infant syndrome) due to acid maltase deficiency.
   (a) *Infantile form* – Heart, liver and muscles involved with failure to thrive and death within first year.
   (b) *Childhood and adult varieties* – Glycogen accumulation only in skeletal muscle. Slowly progressive limb-girdle syndrome, often with hypertrophy of lower limbs. Respiratory muscle involvement in 50%, and often causes death.
2. ***Limb-girdle myopathies*** – Relatively late-onset myopathy.
   (a) *Benign acid maltase deficiency* – with glycogen storage in childhood, adolescence or early adulthood.
   (b) *Carnitine deficiency* – (i) Systemic deficiency – Intermittent attacks of hepatic enlargement and insufficiency, associated with hypoglycemia and encephalopathy. Pre-myopathic phase of 2–10 years before onset of muscle weakness. (ii) Muscle carnitine deficiency – Presents as limb-girdle syndrome in childhood or early adult life, and is progressive. Cardiac involvement is cause of death in later stages.
   (c) *Mitochondrial disorders* – usually result of disorders of respiratory chain function. Late-onset limb girdle myopathy sometimes accompanied by prolonged paralytic attacks (at times involving bulbar and ventilatory functions) and precipitated by exercise, exposure to cold or excessive alcohol intake. 'Ragged red' fibre appearance on muscle biopsy.
3. **Exercise-induced cramps with myoglobinuria** – at rest or on exertion. *Types* – (i) Myophosphorylase deficiency with defect in glycolysis (McArdle's disease). Cramping pains on exercise. (ii) Carnitine palmitoyl transferases (CPTI and II deficiency) – causing defective fatty acid oxidation. Late onset cramps (more than 3 hours after exercise). (iii) AMP deaminase deficiency – Disorder of purine nucleotide metabolism. Occasional cases (including families).
4. ***Chronic progressive ophthalmoplegia plus (CPEC+)*** – Most disorders associated with 'mosaic' cytochrome oxidase deficiency. Generalized disorder with involvement of extra-ocular muscles and limb girdles (mildly). Mitochondrial cytopathy is common to all clinical syndromes.

ENDOCRINE MYOPATHIES

1. *Acromegaly* – A mild myopathy may develop in long-standing cases.
2. *Hyperthyroidism* – (a) Proximal myopathy common. (b) Myasthenia gravis is an uncommon complication. (c) Chronic thyrotoxic myopathy is associated

Table 72: Muscle cramps or pain on exercise
• Disorders of glycogenolysis or glycolysis (e.g. McArdle's disease).
• Mitochondrial myopathies, including zidovudine toxicity.
• Toxic myopathy caused by drugs.
• Dermatomyositis.
• Myopathy caused by deficiency of carnitine palmitoyl transferase.
• Hypothyroid myopathy.

Table 73: Myoglobinuria
• Disorders of glycolysis or glycogenolysis.
• Carnitine-palmitoyl transferase deficiency.
• Malignant hyperthermia crisis.
• DMD after anaesthetic exposure.
• Acute alcoholic myopathy.
• Acute viral myositis.

Table 74: Early or prominent bulbar muscle weakness
• Mitochondrial myopathies – external ophthalmoplegias.
• Oculopharyngeal dystrophy – blepharoptosis, EOP, dysphagia.
• Myotonic dystrophy – temporal m. wasting, facial diplegia, blepharoptosis.

Table 75: Clinical myotonia
• Myotonic dystrophy (adults).
• Myotonia congenita.
• Paramyotonia congenita.
• Myxoedema myopathy.

Table 76: Respiratory insufficiency
• Adult-onset maltase deficiency.
• Acute myopathy after high-dose corticosteroids and muscle paralysing agent.
• Myotonic dystrophy.
• Nemaline myopathy.
• Myopathy with cytoplasmic bodies.

with fasciculations and hyperactive tendon reflexes. (d) Attacks of hyperkalaemic periodic paralysis may occur.

Primary hyperparathyroid myopathy is limb girdle muscle disease in patients with muscle weakness and exaggerated reflexes. It is completely reversible with surgery of parathyroid adenoma

3. *Hypothyroidism* – may be associated with mild proximal weakness, muscle cramp, slowness of contraction, myooedema and delayed tendon reflexes.
4. *Cushing's syndrome and steroid myopathy* – present with proximal weakness, often confined to lower limbs.
5. *Primary hyperaldosteronism* – Episodes of prolonged and severe weakness associated with hypokalaemia.

TOXIC MYOPATHIES

1. Alcohol – (a) *Acute alcoholic myopathy* – induced by heavy drinking in chronic alcoholics. Presents with acute muscle pain, tenderness and weakness, sometimes associated with myoglobinuria, hyperkalaemia and renal impairment. (b) *Subacute alcoholic myopathy* – presents insidiously with proximal weakness often confined to lower limbs.
2. Drug-induced myopathies – (a) *Mechanism unknown* – Heroin, amphetamine, clofibrate, chloroquine, aminocaproic acid, vincristine, cimetidine, isoetharine, statins, steroids, phencyclidine. (b) *Due to marked hypokalaemia* – Diuretics, purgatives, liquorice, carbenoxolone, amphotericin B.

Distinguishing clinical features of common myopathies (Tables 72 to 76).

Investigations

1. *Serum creatine kinase* (SCK) – if elevated indicates muscle damage or necrosis. Very high values in DMD dysferlinopathy and some metabolic myopathies (malignant hyperthermia, acute alcoholic myopathies).
2. *EMG and nerve conduction studies* – confirm the diagnosis of either a myopathy and/or neuropathy.
3. *Muscle biopsy* – provides conclusive evidence.
4. *Molecular genetic analysis* – can diagnose symptomatic and presymptomatic hereditary diseases. It can also detect carriers and be suitable for prenatal diagnosis.
5. *Muscle imaging by CT or MRI* – can establish the distribution and degree of involvement in individual muscles This may be diagnostically helpful or indicate a suitable site for biopsy. In vivo ^{32}P or proton-based magnetic resonance spectroscopy are particularly useful to differentiate some cases of metabolic myopathies from chronic fatigue syndrome and fibromyalgia.
6. *Miscellaneous tests* – Biochemical methods to analyse deficiency states (e.g. glycogenolytic enzyme defects, carnitine deficiency). Immunlogical and serological studies for investigating inflammatory myopathies or retroviral diseases.

Management

1. *Treatment of cause where possible* – e.g. cessation or reduction of corticosteroids together with high protein diet in steroid myopathy, correction of endocrinopathy.
2. *Drug therapy* – In DMD, muscle destruction can be slowed and clinical course stabilised by oral prednisolone or deflazacort 0.75 mg/kg/day. Mexiletine controls myotonia in myotonia congenita and paramyotonia congenita.

   Acetazolamide or spironolactone for preventing acute attacks of hyperkalaemic periodic paralysis. Dantrolene for prevention and treatment of malignant hyperthermia crisis. Some mitochondrial myopathies respond to graded muscle conditioning aided by oral dichloroacetate.

MYOTONIC DISORDERS

Failure of voluntary muscle to relax immediately innervation ceases.

1. *Myotonic Dystrophy* (Dystrophia myotonica):
   (i) *Onset* – Most patients present in adult life with distal weakness and wasting in upper or lower limbs.
   (ii) Muscle weakness/wasting:
      (a) Myopathic facies – Ptosis, hanging jaw, haggard appearance, temporal wasting.
      (b) Weakness of neck flexion, wasting of sternomastoids.
      (c) Distal limb weakness with wasted brachioradialis.
2. Frontal baldness. Hyperostosis frontalis interna.
3. Cataracts (post. subcapsular)
4. Cardiac conduction defects (Heart block, atrial arrhythmias) Cardiomyopathy.
5. Hypoventilation, post-anaesthetic respiratory failure.
6. Hypersomnolence, mental retardation.
7. Hypogammaglobulinaemia.
8. End-organ resistance to insulin (impaired glucose tolerance).
9. Dysphagia, oesophageal dilatation.

   Investigations – (a) CPK - Normal or slightly elevated. (b) EMG - Characteristic myopathic picture with myotonic discharges. (c) Muscle biopsy - Chains of central nuclei, marked variation of fibre size and selective atrophy of type I fibres.

   Treatment – Quality of speech may be improved by procainamide 250 mg t.d.s. or phenytoin 100 mg t.d.s.

1. *Myotonia congenita* – (i) *Thomsen's disease* (AD) - begins in infancy and affects entire voluntary musculature giving rise to generalised muscular stiffness. (ii) *Becker's Disease* (AR) – usually begins later in childhood and is characterized by striking muscular hypertrophy giving the patient a *Herculean appearance.* 'Startle' myotonia may often be present.
2. *Congenital myotonic dystrophy* – can occur in an infant born of a mother with myotonic dystrophy. Features are marked hypotonia, feeding difficulties, areflexia and respiratory insufficiency. About half die in infancy, and those who survive show classical picture of myotonic dystrophy before age of 10.
3. *Paramyotonia congenita* – Generalised myotonia accentuated by cold and accompanied by episodes of weakness related to disturbance of potassium metabolism.

23. MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disease in which antibodies are directed against muscle acetylcholine receptors (AChRs) on the postsynaptic membrane of the neuromuscular junction.

CLASSIFICATION

Myasthenia gravis patients can be divided into antibody-positive and antibody-negative, and into four subgroups that may be useful in determining treatment:

- An early onset group (age <40 years) with hyperplasia of the thymus. HLA B8 and DR3 association and 4:1 female:male ratio
- A late-onset group without thymic hyperplasia, HLA B7 and DR2 association and 1:2 female:male ratio
- Patients with thymoma, who have no HLA association and 1:1 sex ratio
- Patients with ocular myasthenia gravis

PATHOGENESIS

Up to 70% of AChR negative myasthenia patients (seronegative myasthenia gravis) have antibodies to muscles pacific tyrosine kinase MUSK in 85% of patients with generalized disease and in 50% of those with isolated ocular symptoms. Binding leads to down-regulation of AChRs via cross-linking, complement-mediated lysis and possibly direct blockade of AChR function. It is the reduction of functional AChRs that is responsible for the clinical picture.

Transient neonatal myasthenia caused by placental transfer of AChR antibodies occurs in 8% of babies born to mothers with myasthenia gravis.

The thymus gland is thought to have an important role in the pathogenesis. The normal thymus is a source of AChR, and expression may be up-regulated in patients with thymoma. The thymus is also thought to be involved in deleting autoreactive T cells specific for cell antigens, and therefore any disruption of function would allow escape of such cells. In addition, the hyperplastic thymus may be a site of anti-AChR antibody production.

Penicillamine treatment is a rare cause of myasthenia gravis seen in rheumatoid arthritis, and usually resolves on drug withdrawal.

CLINICAL FEATURES

- Ocular muscles – Patients typically present with weakness of ocular muscles causing variable ptosis and diplopia. Up to 20% of cases involve ocular muscles only (ocular myasthenia).
- Fatiguability – Increase in weakness on repeated use of muscles, worsening of weakness towards the end of the day. Improvement in muscle strength after rest are characteristic features.
- Limb weakness – In generalized disease, weakness of the limbs affecting proximal muscles, elbow extension and finger extension is common.
- Facial involvement may cause difficulty with eye closure and a snarling smile, and weakness of jaw muscles difficulty in chewing.
- Trunk involvement can occur.
- Respiratory muscle involvement can be life-threatening. Shortness of breath, particularly on lying flat (diaphragmatic weakness) is common. Reduced arterial oxygen capacity is a late sign of respiratory failure.
- Bulbar symptoms, e.g. nasal speech and nasal regurgitation may occur. Severe dysphagia may necessitate tube feeding.
- Weakness of neck muscles may cause head dropping. Muscle wasting is not a feature, tendon reflexes are well retained.
- Slow ventilatory recovery from general anaesthesia following use of curare-like muscle relaxants can be a first presentation.

Myasthenic crisis. It is characterized by weakness of intercostal and other respiratory muscles. The crisis because of acute respiratory failure.

Precipitating Causes – Intercurrent infection, physical fatigue, emotional stress, pregnancy, use of aminoglycosides, anaesthetic agents causing muscular paralysis.

Diff. Diag. TB syndrome, acute poliomyelitis, other hypercapnia syndromes (if respiratory muscles are chiefly involved, botulism, snake poisoning (krait, cobra bite) acute tubular acidosis (due to severe hypokalaemia), familial periodic paralysis.

Management. Intubation and ventilation, also use of pyridostigmine, steroids, immunoglobulins and even plasmapheresis.

INVESTIGATIONS

Anti-AChR antibodies are detectable in the serum of most patients. A negative result does not exclude the diagnosis, and is common in the pure ocular form.

RNS (Repetitive Nerve Stimulation) – shows decreasing muscle action potential with rapid stimulation. Increased jitter and blocking is found on single-fibre EMG. Abnormal single fibre EMG can be found in motor neuron disease and some myopathies.

Prostigmine test – 1–1.5 mg of prostigmine by IM injection. Improvement in muscle power in 15–30 mts, if patient myasthenic.

Serum AChR antibodies are most commonly associated with thymoma.

Autoantibodies to acetylcholine receptors are positive.

Chest CT/mRI to identify any associated thymoma (Figs. 62 and 63).

Differential diagnosis – Difficulties arise in patients who are antibody negative. (a) Lambert-Eaton myas-

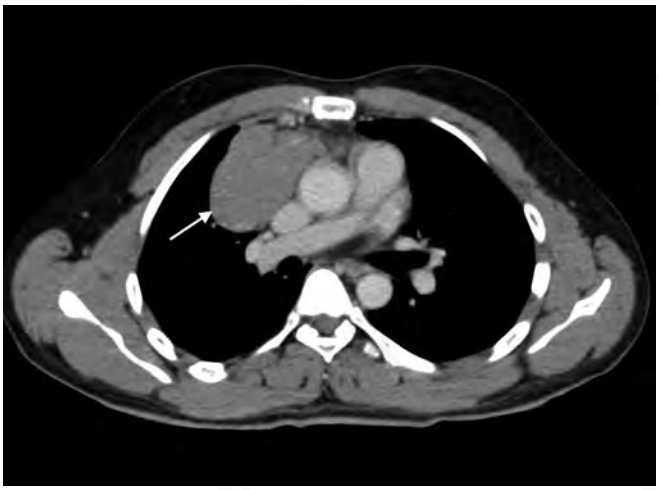


Fig. 62: CECT axial view showing thymoma (arrow)

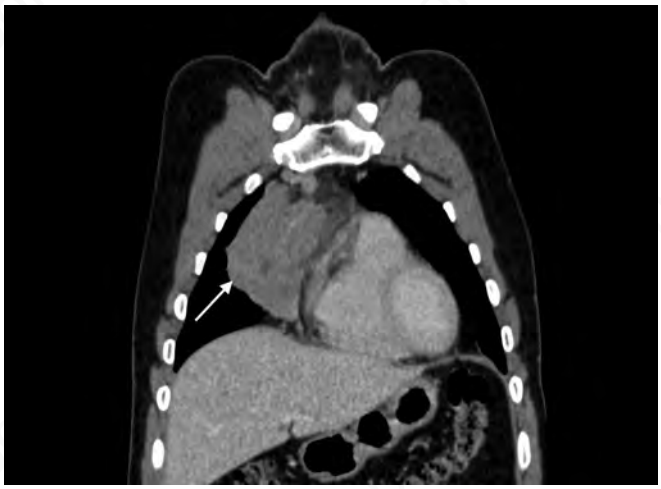


Fig. 63: CECT coronal view showing thymoma (arrow)

thenic syndrome (*see* further). (b) Congenital myasthenic syndromes – should be considered in early-onset cases, particularly those with family history of similar disease. (They do not respond to immunotherapies). (c) Chronic progressive external ophthalmoplegia can mimic ocular symptoms of myasthenia, though fatigue is not typical.

Plus minus lid syndrome with ataxia. It is an acquired neurological abnormality of eyelid position with unilateral ptosis and contralateral eyelid retraction. This association has been described in ocular myasthenia, after lesions of oculomotor nerve, ocular myositis and paramedian mesencephalic diencephalic lesions

MANAGEMENT

Drug Therapy

Anticholinesterase – first line treatment – Pyridostigmine 60 mg qds or Neostigmine 30 mg qds. Cholinergic side-effects (abdominal cramps, diarrhoea) can be controlled with probanthine bromide 15 mg tds. A pyridostigmine replacement of more than 90 mg qds indicates need for immuno-suppression.

Corticosteroids: Prednisolone dose – (a) For myasthenia of ocular muscles 10 mg on alternate days initial, increase by 5 mg every 5 days to dose of 1 mg/kg body weight (b) Azathioprine for steroid sparing effect. Dose 50 mg/d, increased every 2 week by 50 mg till total dose of 2.5 mg/kg. Blood counts and LFTs should be checked once in 2 weeks because of its adverse effects. It takes about 6 months for Azathioprine.

Once there is remission of myasthenia, prednisolone is slowly reduced to 5 mg per dose every month till dose of 20 mg on alternate days, subsequently dose is further reduced by 1 mg per dose every month till the drug is stopped and continue Azathioprine only if possible.

Other drug therapies – if patient responds inadequately to above regimen – (a) *Cytotoxic agents* such as cyclosporine or methotrexate. (b) *Plasma exchange* – 3–5 daily exchanges of 2–3 litres. (c) IV *immunoglobulin* 0.4 g/kg/day for 5 days in myasthenic crisis.

Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab and occasionally cyclophosphamide are effective in many patients, either alone or in various combinations.

Thymectomy

Indications – Patients <40 years of age who have strongly positive antibody test (i.e. high titre of antibodies to acetylcholine receptors) and have thymic hyperplasia on imaging studies. Thymoma is an indication for surgery with or without postoperative radiotherapy to treat the tumour. Thymectomy should be carried out in all patients with generalized MG who are between the ages of puberty and at least 55 years.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is an autoimmune disorder of the presynaptic neuro-muscular junction caused by antibodies to the voltage-gated calcium channels situated at the nerve terminus.

Aetiology and pathogenesis – LEMS is more common after age of 50; 60% cases are associated with small cell lung cancer. A predisposition to other autoimmune diseases is also seen.

Antibodies to P/Q-type voltage-gated calcium channels on the presynaptic membrane of the neuromuscular junction are detectable by radioimmunoprecipitation assay in 95% of patients. Association with small lung cell cancer is thought to result from crossreactivity of autoantibodies to voltage-gated calcium channels on the malignant cells with those situated at the neuromuscular junction.

Clinical features – (a) Proximal muscle weakness is the most common presentation. It may be followed by upper limb weakness. (b) Autonomic symptoms – Dry mouth, constipation, impotence. (c) Diplopia is uncommon and tendon reflexes tend to be exaggerated particularly in lower limbs in contrast to myasthenia gravis.

Investigations – Highly specific voltage-gated calcium channel antibodies are detectable in the serum in most patients. Compound action muscle potentials are reduced and increase by more than 100% after high-frequency nerve stimulation or maximal voluntary contraction. (c) Chest CT for small lung cancer.

Management – 3,4-diaminopyridine (3,4-DAP) qds. usually improves symptoms in most patients. Immunosuppression is effective in non-cancer LEMS. Azathioprine is contraindicated in presence of malignancy. Treatment of the tumour can lead to resolution of LEMS. Plasma exchange and immunoglobulin can be useful in treatment of severe symptoms, but the effect wears off after a few weeks.

24. MUSCULAR WASTING

Table 77 lists the causes of muscle wasting.

Table 77: Causes of muscle wasting

A. Neuromuscular causes
1. ***Primary muscular diseases***
(a) Muscular dystrophies (LGMD, DMD, BMD, myotonic dystrophy).
(b) Inflammatory muscle diseases – Polymyositis, dermatomyositis.
2. ***Anterior horn cell diseases***
(a) Motor neuron disease (ALS, progressive muscular atrophy).
(b) Benign focal amyotrophy (monomelic amyotrophy), spinal muscular atrophy (Werdnig- Hofmann, Welander, Adult SMA, bulbospinal atrophy.
(c) Infection like poliomyelitis, West Nile fever.
3. ***Root lesions*** – Radiculopathies due to spondylosis, spinal neoplasms.
4. ***Plexopathies*** – Idiopathic brachial plexopathy (Parsonage Turner syndrome), radiation plexopathy, diabetic lumbosacral plexopathy (diabetic amyotrophy).
5. ***Neuropathies***
(a) Axonal neuropathies, e.g. HMSN 2, Axonal GBS.
(b) Compression neuropathies, e.g. carpal tunnel syndrome leads to ulnar wasting, ulnar neuropathy at elbow leads to hypothenar and interossei wasting, common peroneal neuropathy at fibular head (peroneal muscle wasting).
(c) Infection like leprosy leads to wasting in distribution of affected nerve.
6. ***Myoneural junction disorder*** – Myasthenia gravis (muscular wasting very rare).
B. Disuse atrophy
(a) In UMN lesions, e.g. strokes, cerebral neoplasms.
(b) Due to pain as in arthritis, following fracture.
C. Systemic generalized wasting – HIV, malignancy, thyrotoxicosis, TB.

INVESTIGATION OF A CASE OF MUSCULAR WASTING

I. History

1. ***Family history*** – in Autosomal dominant disease, e.g. HMSN.
2. ***Age of onset*** – Muscular dystrophy, poliomyelitis and diphtheritic paralysis in infancy and childhood; motor neuron disease in second half of life, peroneal muscular atrophy and wasting of cervical rib presents in early adult life, cervical spondylosis usually after 45.
3. ***Mode of onset*** – Rapid in poliomyelitis and acute radiculitis. More gradual in diphtheritic paralysis, cervical spondylosis or tumour, and infective polyneuritis. In spinal lesions, atrophy usually precedes weakness, in polyneuritis, weakness precedes atrophy.
4. ***Symmetry*** – Symmetric and proximal in muscular dystrophies, symmetric and distal in axonal neuropathies.
5. ***Asymmetry*** – in MND, benign focal amyotrophy, radiculopathy.
6. ***Progressive*** – Muscular dystrophies, MND, hereditary neuropathies.
7. ***Static*** (following an initial progression) – Axonal GBS, monomelic amyotrophy.
8. ***Associated discomfort*** – Muscle pain – at rest can occur in polymyositis, polymyalgia rheumatica, acute myoglobinuric myopathy and in myopathies of metabolic bone disease. Episodic pain, which may at times be associated with weakness, suggests a metabolic disorder. Pain that develops during exercise is considered to be characteristic of McArdle's disease, though it can occur in other metabolic myopathies (e.g. mitochondrial myopathies). Pain that follows exercise by a few hours usually occurs in disorders of lipid metabolism.

II. Examination

1. ***Distribution of wasting***:
   (a) *Proximal wasting* – Muscular dystrophies, lumbosacral plexopathy, brachial plexopathy.
   (b) *Symmetric distal wasting* – Calf, hand and forearm wasting in axonal neuropathies.
   (c) *Wasting of small muscles of hand* – C8 to T1 radiculopathy, syringomyelia, lower cervical cord tumors, onset of MND, distal muscular dystrophies, carpal tunnel syndrome (wasting of thenar muscles), ulnar neuropathies (wasting of interossei and lumbricals III and IV), multifocal motor neuropathy with conduction block. Lower brachial plexus lesions (radiation or tumors).

(d) *Wasting of legs* – Peroneal muscle wasting in pseudoneuritic presentation of MND, common peroneal neuropathy, HMSN, cauda lesions, L5-S1 radiculopathy.

(e) *Cranial muscle atrophy* – FSHD, oculopharyngeal muscular dystrophy, MD.

2. ***Pseudohypertrophy*** – BMD, DMD, myotonia congenita.
3. ***Muscle tenderness*** – None in dystrophy, motor neuron disease, and syringomyelia. In arthritic atrophy and cervical rib pressure, affected muscles are tender to pressure while the wasting process is active. In carpal tunnel syndrome production of typical symptoms by digital compression of median nerve in region of transverse carpal ligament or by forcible flexion of the wrist for one or two minutes.
4. ***Fasciculations*** – Absent in MND, monomelic amyotrophy, syringomyelia, radiculopathy. Fasciculatory tremors in neuropathies.
5. ***Myotonia*** – in myotonic dystrophy. In longstanding cases however, grip myotonia may not be evident because of progressive wasting.
6. ***Evidence of other signs of diseases in the nervous system*** – (i) Monoplegia or hemiplegia in disuse or postparalytic atrophy. (ii) Bulbar paralysis in motor neuron disease. (iii) Pain in neck and shoulder in radiculitis. (iv) CSF changes in spinal block. (v) Treponemal antibodies in syphilitic amyotrophy. (vi) Blue line on gums, and anemia in lead poisoning.
7. ***Thickening of peripheral nerves*** – (a) Single nerve thickening in neoplastic process, e.g. neurofibroma, Schwannoma, malignant nerve sheath tumour, localized peripheral hypertrophic neuropathy. (b) Generalized thickened nerves – Leprosy, acromegaly, neurofibromatosis, amyloidosis, chronic inflammatory demyelinating polyradiculoneuropathy, peroneal muscular atrophy, lymphoma infiltration, Refsum's disease.
8. ***Sensory loss*** – Glove and stocking in axonal neuropathy, radicular distribution in radiculopathies, in nerve distribution in ulnar, median, common peroneal neuropathies. Dissociated sensory loss in syringomyelia. No sensory loss in ALS.
9. ***Reflexes*** – Absent or depressed reflexes in upper limbs and present in lower limbs in syringomyelia. Exacerbated in presence of wasting in ALS. Absent in radiculopathies in the involved segment. Absent ankle reflex in axonal neuropathies.

III. Investigations

1. ***Haematological and biochemical*** – to demonstrate nature of primary disorder to which muscular wasting is secondary in case of systemic, inflammatory or metabolic disease.
2. ***Serum creatine kinase*** (CK) – Very high levels in Duchenne and Becker dystrophies, acute polymyositis, and acute myoglobinuric myopathies. In other myopathies it may be normal or only moderately raised.
3. ***EMG*** – Large, wide polyphasic motor unit potentials in neuropathic wasting; small, short, polyphasic potentials in myopathic wasting.
4. **NCS** – Small compound muscle action potential amplitude in axonal neuropathies. Normal in myopathies.
5. **Muscle biopsy and immunochemistry** – Normal in muscular dystrophies, polymyositis, dermatomyositis. Neurogenic atrophy can be confirmed in case of doubt.

25. PERIPHERAL NEUROPATHY

PATHOPHYSIOLOGY

A peripheral nerve comprises about six fascicles, each containing many myelinated and unmyelinated axons. Each fascicle has small nutrient blood vessels integral to the function of the nerve. Disorders of peripheral nerves can primarily damage myelin (e.g. Guillain-Barre syndrome) or the axons (e.g. vincristine, other drugs), or interfere with blood supply of the nerve leading to areas of necrosis in the distribution of small nutrient vessels (e.g. polyarteritis nodosa), vasculitis.

Many toxic processes that produce slowly progressive damage to nerve cell bodies lead to a 'dying-back' type of neuropathy, in which the longest axons show damage initially and neuropathic symptoms ascend from the feet, i.e. distal to proximal progression.

Some pathological processes selectively affect small unmyelinated nerves (e.g. alcohol, amyloid), leading to characteristic autonomic disturbances and pain seen in these neuropathies. Vasculitic disorders often lead to multiple, random pathologic lesions within the nerve (mononeuritis multiplex).

CLASSIFICATION

Peripheral nerve disease can be classified according to – (a) Clinical classification, (b) Generalized neuropathy, whether pathological process is axonal or demyelinating. (c) Predominantly sensory or predominantly motor forms.

A. Clinical Classification

1. ***Mononeuropathy or focal neuropathy*** – Single nerve involved.
   (a) Compression – e.g. compression of radial nerve against humerus (Saturday night palsy).
   (b) Entrapment.

   Carpal tunnel syndrome – Compression of median nerve as it passes through the carpal tunnel in the flexor retinaculum at the wrist. *Causes* – (i) Wrist fracture. (ii) Arthritis of the wrist particularly RA. (iii) Soft tissue thickening in myxoedema and acromegaly. (iv) Oedema, notably associated with pregnancy. Obesity. (v) No obvious cause. More common in women. *Symptoms* – Pain, numbness and paraesthesiae in the hand. Pain may radiate through forearm and occasionally involve the whole arm. Typically pain is most troublesome at night or first thing in morning. *Signs* – Weakness of abductor pollicis brevis, with or without wasting, and also weakness of opponens. Sensory impairment – of median distribution. Positive Tinel sign – Gentle tapping over carpal tunnel causes paraesthesiae in part of the cutaneous distribution of the nerve. Phalen's sign – Carpal tunnel symptoms on holding wrist flexed at 90° for one minute.

   Treatment – (i) Mild case – Wrist splint, diuretics and injection of hydrocortisone into carpal tunnel may give temporary relief. (ii) In severe case – Surgical decompression of carpal tunnel.

   Common peroneal nerve palsy – The common peroneal nerve at the fibula head is a common site of entrapment. *Causes* – Focal presentation of more generalized neuropathy, individuals who have sat with their legs crossed for a long period (e.g. during airline flight), or sitting from a kneeling position. *Clinical features* – Patient develops foot drop and variable sensory loss in outer border of the foot and lateral aspect of lower leg. *Management* – If the disorder is confined to a demyelinating lesion, recovery occurs within 1 or 2 weeks. Continued pressure on the nerve leads to axonal damage, recovery may take several months. Surgery is seldom of benefit.
   (c) Other causes – Trauma, fractures, operations, penetrating injuries, lacerations and injections.
2. ***Multifocal neuropathy*** – More than one and at times many individual nerves affected in a patchy asymmetric distribution – mononeuritis multiplex.

Causes

(a) *Vascular* – Diabetes, rheumatoid arthritis, polyarteritis nodosa, SLE, Wegener's granulomatosis, non-systemic vasculitis, Lyme disease.
(b) *Infections* – Leprosy, HIV.
(c) *Physical injury* – Repeated flexion extension of wrist (while typing), due to hand held vibrating instruments.
(d) *Inflammation* – Sarcoidosis.
(e) *Demyelination* – Multifocal motor neuropathy with conduction block (MMN), multifocal acquired damage demyelinating sensory and motor neuropathy (MADSAM).
(f) *Familial disposition* – to entrapment neuropathy (tomaculous neuropathy).

Generalized Neuropathy

Diffuse symmetrical involvement of peripheral nerves. Some diseases, e.g. diabetes, may also produce a multifocal neuropathy. Some neuropathies also affect spinal roots (polyradiculoneuropathy). Common causes are – Leprosy, diabetes mellitus, chronic kidney failure, G-B syndrome, INH toxicity (Table 78).

Table 78: Causes of peripheral neuropathy

1. **Toxins**	
– Alcohol.	
– Heavy metals and industrial agents – Arsenic, lead, mercury, thallium, gold, acrylamide, n-hexane, methyl n-butyl ketone, tri-orthocresyl phosphate, carbon disulphide.	
– Drugs	Amiodarone
Isoniazid	Metronidazole
Nitrofurantoin	Lithium
Vincristine	Cyclosporine
Dapsone	Gold
Chloroquine	Stavudine
Statins	Didanosine
2. **Avitaminosis** – Beriberi, pellagra, vitamin B_{12} deficiency, burning feet syndrome, vitamin E deficiency.	
3. **Metabolic and endocrine disorders** – Diabetes, gout, myxoedema, acromegaly, amyloid disease, uraemia, porphyria, copper deficiency.	
4. **Infections**	
(a) *Systemic* – (i) *As a complication* – Diphtheria, tetanus, typhoid, parainfectious, mumps, staphylococcal septicaemia, measles, influenza, tuberculosis, meningitis, infectious mononucleosis, brucellosis, HIV. (ii) *As the main symptom* – Acute inflammatory polyneuropathy, 'rheumatic' polyneuritis, brachial neuritis, polyneuritis with parotitis and iridocyclitis.	
(b) *Local infections of nerves* – Leprosy.	
5. **Collagen and allied disorders** – Polyarteritis nodosa, sarcoidosis, disseminated lupus erythematosus, rheumatoid polyneuritis.	

Contd...

Contd...

6. **Malignancy** – Carcinoma especially of lung, lymphoma, leukaemia. Malignant inflammatory sensory polyganglionopathy. Paraneoplastic vasculitic neuropathy.
7. **Paraproteinaemias and dysproteinaemias** – Multiple myeloma, cryoglobulinaemia, benign monoclonal gammopathy, primary amyloidosis (AL and AF).
8. **Hereditary** – Charcot-Marie-Tooth (CMT) disease, Peroneal muscular atrophy (HMSN type I, II, III, IV), Friedreich's ataxia, familial dysautonomia (Riley-Day), metachromatic leucodystrophy, Fabry's disease (Angiokeratoma corporis diffusum). Hypertrophic neuropathy (Dejerine-Sottas disease), hereditary sensory neuropathy, hereditary ataxic neuropathy (Refsum's syndrome), abetalipoproteinaemia.
9. **Polyneuritis of obscure origin (cryptogenic neuropathy)**: Recurrent polyneuritis.

Table 79: Causes of demyelinating neuropathy

Acute
• Guillain-Barre syndrome
Chronic
Hereditary
• Hereditary motor and sensory neuropathy types I, III, IV
• Refsum's syndrome
• Metachromatic leucodystrophy
• Cockayne's syndrome
Paraproteinemia
• Myeloma
• Waldenstrom's macroglobulinemia
• Monoclonal gammopathy of undetermined significance
Drugs
• Amiodarone
• Perhexiline
Chronic inflammatory demyelinating neuropathy

Symptoms

1. *Sensory* – (a) *Subjective disturbances* – Numbness, tingling, feelings of pins and needles in hands and feet, burning sensations, pain in the extremities, sensation of walking on cotton wool or band-like constrictions around wrist or ankles, unsteadiness on the feet and tumbling (ataxia). (b) *Objective sensory loss* – Bilaterally symmetrical, impairment of all forms of sensation; glove and stocking type of anaesthesia. Preceding the anaesthesia, there is hyperaesthesia. Tenderness of calf muscles and sometimes nerves.
2. *Motor* – Major symptom is weakness. Wasting and weakness most marked initially in the limbs, involving lower limbs before upper. Predominantly proximal weakness as in Guillain-Barre syndrome. Fasciculations may be seen, usually in patients with rapidly progressive denervation.
3. *Autonomic disturbances* – Dryness or excessive sweating of the extremities, postural hypotension, impotence and sphincter disturbances, diarrhoea and constipation.
4. *Bulbar dysfunction* – can follow cranial nerve involvement in some peripheral neuropathies. Double vision, respiratory problems and difficulties with swallowing and speech may occur.

Signs

- Wasting and weakness – in distal muscles of hand and feet.
- Absent or reduced reflexes
- Signs of autonomic disturbance (e.g. postural hypotension)
- Sensory loss – Small fibre type involving pain and heat sensation, or large-fibre type with loss of fine touch or pin-prick sensation or two point discrimination.
- Cranial nerve examination may reveal facial weakness and ptosis
- Vital capacity may be reduced
- Trophic changes – Skin glossy, furrowing and falling off of nails, cold extremities

C. Demyelinating Neuropathy

Table 79 for the causes of demyelinating neuropathy.

D. Axonal Neuropathy

Table 80 for the causes of axonal neuropathy.

Table 81 gives the differentiating features between demyelinating and axonal neuropathy.

Table 82 for the clinical types of neuropathies.

INVESTIGATIONS

Nerve conduction studies – determine whether the process is axonal or demyelinating and whether there is conduction block. Conduction block is characteristic of chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy. Nerve conduction studies also provide information on whether the process is generalized or focal, and may reveal specific site of damage in focal entrapment neuropathies (Table 83).

Nerve biopsy – Sural nerve (or radial nerve) biopsy is usually helpful in leprosy, giant axonal neuropathy. Nerve biopsy is also indicated in suspected vasculitic neuropathies or in the diagnosis of amyloid (AL and AF).

Table 80: Causes of axonal neuropathy

Acute	
• Toxins	
• Porphyria	
• Vasculitic disease (SLE, PAN)	
Chronic	
Metabolic	*Autoimmune diseases*
• Diabetes	• RA
• Uraemia	• SLE
Deficiencies	*Hereditary*
• Vitamin B_{12}	• Hereditary motor and sensory neuropathy type II
• Thiamine	
• Vitamin E	
• Nicotinamide	• Giant axonal neuropathy
Toxic	• Hereditary ataxias
• Alcohol	
• Drugs	
Leprosy	
Paraneoplastic	*Miscellaneous*
• Lymphoma	• Chronic obstructive airway disease
• Carcinoma of lung	
• Polycythemia rubra vera	• Primary amyloid
	• Sarcoid

Other investigations – should include:

- Blood glucose, glucose tolerance test
- Vitamin B_{12}
- ESR
- Full blood count
- Serum protein electrophoresis (to exclude myeloma and other paraprotein- associated neuropathies)
- Chest radiograph (neoplasm)

MANAGEMENT

1. *General* – (i) Elimination of possible toxic or infectious cause. (ii) Control of any existing metabolic or nutritional deficiencies – correction of anaemia with iron or vitamin B_{12}, high protein diet, multivitamins.
2. *Local measures* – Occupational therapy helps maintain full use of weak muscles. Physiotherapy helps stimulate recovery and maximum gain of function. Foot deformity requires attention to footwear and appropriate orthotic aids.

Table 81: Differentiation between demyelinating and axonal neuropathy

Features	*Demyelinating neuropathy*	*Axonal neuropathy*
Onset	Acute or insidious	Insidious
Sensory loss	Minimal	Glove and stocking anaesthesia
Deep reflexes	All DTRs loss	Loss of only ankle reflexes
Progress	Recovery within few weeks	Recovery, if at all over months or years
Central involvement	Rare	Can occur
Nerve conduction	Increased	Normal

Table 82: Clinical types of neuropathies

Acute onset	
• Guillain-Barre	• Serum sickness
• Porphyria	• (Post-vaccinal)
• Diphtheria	• Malignancy
• Toxic	• Critical illness polyneuropathy
Predominantly motor	
• Guillain-Barre	• Lead
• Porphyria	• Botulism
• Diphtheria	• Charcot-Marie-Tooth disease
Predominantly sensory	
• Leprosy	• Hereditary sensory neuropathies (HSAN)
• Diabetes	
• Vitamin B_{12} or B_1 deficiency	
• Malignancy	• Uraemia (early stages)
	• Amyloid disease
	• Lyme disease.
Painful neuropathies	
• Alcohol, nutritional deficiencies	• Thallium poisoning
• Diabetic neuropathy	• Cryoglobulinemia
	• Lyme disease
• Hereditary sensory neuropathy	• AIDS-related neuropathy
• Drug-induced	
Predominant upper limb involvement	
Diphtheria	
Porphyria	

Contd...

Contd...

Lead	
MMN	
With associated hypertension	
GB syndrome	
Polyarteritis nodosa. Lead poisoning	
Porphyria (acute intermittent)	
Cr. nerve involvement in peripheral neuropathy	
Guillain Barre (VI, VII)	
Miller-Fisher variant (III, IV, VI)	
Diabetes (III, VI)	
Sarcoidosis (VII).	
Leprosy [VII, V (sensory)]	

3. *Specific* – e.g. vitamin B_1 for thiamine deficiency, adequate control of diabetes, etc. Corticosteroids may be helpful in chronic relapsing demyelinating neuropathies and some patients may respond to immunosuppressive and cytotoxic drugs and to plasmapheresis.

INHERITED NEUROPATHIES

Peroneal Muscular Atrophy

(Charcot-Marie-Tooth disease, CMT)

Most common hereditary motor and sensory neuropathy. Types I and II are most common varieties.

CMT type I – is a demyelinating usually autosomal dominant neuropathy. At least 70% of cases are caused by duplication of a stretch of DNA on chromosome 17 encoding a myelin protein (PMP22). It characteristically presents with foot drop in early childhood and weakness of the legs, some develop mild weakness in the hands. Sensory loss is mild. Nerve conduction studies show severely reduced peripheral conduction.

CMT type II – is an axonal disease dominant or recessive. Presentation is similar to type I, though the disorder may produce more extensive wasting.

INFLAMMATORY DEMYELINATING POLYNEUROPATHIES

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) (Guillain-Barre Syndrome)

Guillain-Barre syndrome is an acute, predominantly motor neuropathy, which progresses to its peak in less than 4 weeks. It is a clinical syndrome with a number of subtypes:

- Guillain-Barre syndrome
  - Acute inflammatory demyelinating polyneuropathy
  - Acute motor axonal neuropathy
  - Acute motor and sensory axonal neuropathy
- Miller-Fischer syndrome
  - Subacute inflammatory demyelinating neuropathy
  - Chronic inflammatory demyelinating neuropathy (CIDP)

Patient with progressive neuropathy over 8 weeks have CIDP.

Table 83: NCV and EMG studies in delyelinating vs axonal neuropathy

	Axonal segmental degeneration	*Segmental degeneration demyelination*
Motor nerve conduction studies		
CMAP amplitude	Decreased	Normal
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Conduction block	Absent	Present
Temporal dispersion	Absent	Present
F-wave	Normal or absent	Prolonged or absent
H-reflex	Normal or absent	Prolonged or absent
Sensory nerve conduction studies		
SNAP amplitude	Decreased	Normal or decreased
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow
Needle EMG		
Spontaneous activity		
Fibrillations	Present	Absent
Fasciculations	Present	Absent
Motor unit potential		
Recruitment	Decreased	Decreased
Morphology	Long duration/ polyphasic	Normal

Aetiology – *Age* – usually 15–40 years. Sex – Male female ratio 1.5:1. *Antecedent infection* – usually upper respiratory tract infection or GI illness in about 70%. Infectious agents commonly identified are Campylobacter jejuni and cytomegalovirus.

Pathogenesis – Probably a cell-mediated immune response to preceding infection.

Clinical Features

Prodromal stage – Headache, vomiting, slight fever, pain in back and limbs.

Latent period – Few days to several weeks; may be absent.

Stage of paralysis – Patient may come in this stage, the initial stage being absent. Alarming clinical picture with motor weakness progressing to paralysis and various sensory disturbances.

Diagnosis

A. Clinical

1. *Motor symptoms* – Onset of paralysis sudden or gradual. Proximal weakness is more than distal. Headache and fever. All four limbs may be paralysed simultaneously or first lower and then upper. Proximal and distal segment muscles affected equally. Involvement of muscles of neck and trunk. Dysphagia and ophthalmoplegia. Loss of superficial and deep reflexes.
2. *Sensory symptoms* – Pain, radicular involving most commonly the proximal portions of the limbs, numbness and tingling of limbs. Sensations may be impaired at the periphery, and muscles may be tender.
3. *Cranial nerve paralysis* – Facial, neck and bulbar muscle paralysis common, and weakness of extraocular muscles may also occur.
4. *Reflexes* – usually depressed or absent.
5. *Sphincters* – rarely involved.
6. *Symptoms of toxaemia* – Fever, rash, leucocytosis, are usually absent.

B. CSF

Protein levels usually increased (sometimes up to 6 g/litre). Some patients may have normal levels in the first week,

C. Nerve conduction velocity studies

Typical early findings are prolonged distal motor latencies in either upper or lower limbs, prolonged F wave latencies and low muscle action potential amplitudes (CMAP). Slowing of nerve conduction indicating demyelination is seen late.

Diagnostic Criteria

Table 84 for the Asbury's criteria and Table 85 for the Brighton criteria.

Management

Respiratory Care

- Monitor vital capacity (not peak flow) 4-hourly.
- If <1 litre, check accuracy (ensure air is not escaping because of facial weakness, check patient technique). If accurate consider urgent ventilation
- If < 1.5 litre but falling, shift to ICU
- Positive pressure ventilation and chest physiotherapy

Cardiac Care

Institute cardiac monitoring – if evidence of bradycardia (heart rate < 50), particularly following tracheal suction, consider temporary cardiac pacing.

Table 84: Asbury's criteria for Guillain-Barre syndrome

A. **Features required for diagnosis** 1. Progressive motor weakness of more than one limb (can progress to total paralysis of all four extremities). 2. Areflexia
B. **Features strongly supporting the diagnosis**
(a) *Clinical features.* 1. Progression of symptoms and signs over days up to 4 weeks. 2. Relative symmetry of symptoms. 3. Mild sensory symptoms or signs. 4. Cranial nerve involvement, especially facial diplegia. 5. Recovery beginning 2–4 weeks after progression ceases. 6. Autonomic dysfunction. 7. Absence of fever at onset of illness
(b) *CSF picture* 1. Elevated CSF protein after one week of symptoms. 2. Cell counts of >10 mononuclear leucocytes per cmm of CSF.
(c) *Electrodiagnostic studies* Evidence of nerve conduction slowing or block.
C. **Features making the diagnosis doubtful** 1. Marked persistent asymmetry of weakness. 2. Marked bladder or bowel dysfunction at onset or its persistence thereon. 3. Presence of polymorphonuclear leucocytes or >50 mononuclear leucocytes per cmm of CSF. 4. Sharp sensory level.
D. **Features excluding the diagnosis** 1. Diagnosis of acute intermittent porphyria or recent diphtheria infection. 2. Diagnosis of botulism, poliomyelitis, hysterical paralysis, toxic neuropathy. 3. Purely sensory syndrome.

Table 85: Brighton criteria for diagnosis of Guillain-Barre syndrome (GBS) and Miller-Fisher syndrome

Clinical case definitions for diagnosis of GBS
Level 1 of diagnostic certainty
Bilateral AND flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Electrophysiologic findings consistent with GßS
AND
Cytoalbuminologic dissociation (i.e. elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/µL)
AND
Absence of an identified alternative diagnosis for weakness
Level 2 of diagnostic certainty
Bilateral AND flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
CSF total white cell count <50 cells/µL (with or without CSF protein elevation above laboratory normal value)
OR
If CSF not collected or results not available, electrophysiologic studies consistent with GBS
AND
Absence of identified alternative diagnosis for weakness
Level 3 of diagnostic certainty
Bilateral and flaccid weakness of the limbs
AND
Decreased or absent deep tendon reflexes in weak limbs
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Absence of identified alternative diagnosis for weakness

Contd...

Contd...

Clinical case definitions for diagnosis of Miller fisher syndrome
Level 1 of diagnostic certainty
Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND
Absence of limb weakness
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
Cytoalbuminologic dissociation (i.e., elevation of cerebrospinal protein above the laboratory normal and total (CSF white cell count <50 cells/µL)
AND
Nerve conduction studies are normal OR indicate involvement of sensory nerves only.
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis
Level 2 of diagnostic certainty
Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND
Absence of limb weakness
AND
Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
CSF with a total white cell count <50 cells/µL) (with or without CSF protein elevation above laboratory normal value)
OR
Nerve conduction studies are normal OR indicate involvement of sensory nerves only
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis
Level 3 of diagnostic certainty
Bilateral ophthalmoparesis and bilateral reduced or absent tendon reflexes and ataxia
AND
Absence of limb weakness
AND

Contd...

Contd...

Monophasic illness pattern and interval between onset and nadir of weakness between 12 h and 28 days and subsequent clinical plateau
AND
No alterations in consciousness or corticospinal tract signs
AND
Absence of identified alternative diagnosis
Course – Within a period of 3 weeks, it progresses to maximum disability, often with complete quadriparesis and respiratory paralysis. Recovery without significant disability occurs in about 80%, subsequent relapses occur in about 5% of patients.

Prevention of Thrombosis and Limb Deformity

Give subcutaneous heparin and apply anti-embolism stockings.

Pay special attention to position of limbs.

Active Treatment

- Intravenous human immunoglobulin 0.4 g/kg/day for 5 days
- If deterioration continues, consider further IV immunoglobulin or
- Plasma exchange (50 mL/kg on five occasions over 7–10 days)

Miller-Fisher syndrome – Triad of ophthalmoplegia, ataxia and areflexia without weakness. It is considered to be a variant of GB syndrome. Antibodies to ganglioside GB are seen in 90% of patients. Recurrences are rare.

Chronic inflammatory demyelinating polyneuropathy (CIDP) – is a subacute or chronic progressive demyelinating neuropathy.

Progression over 2 months distinguishes it from G-B syndrome. The disorder is associated with increased frequency of HLA DR3, indicating that the disease may result from an aberrant immune response leading to a chronic form of G-B syndrome.

Management of CIDP and Miller-Fisher syndrome – Corticosteroids, plasma exchange and IV IG in combination are effective. Azathioprine and other immunosuppressive agents are usually needed as corticosteroid-sparing agents.

Vasculitic neuropathies – in systemic disorders such as RA and PAN which produce a number of different lesions within the nerve and are hence termed multifocal. Because of the multifocal onset, the combination of individual peripheral nerve involvement is called 'mononeuritis multiplex'. *Diagnosis* – High ESR or positive antinuclear factor or antinuclear cytoplasmic antibody. Nerve biopsy reveals patchy multifocal process with inflammatory cells.

Multifocal motor neuropathy – resembles CIDP, but does not respond well to steroids. It has considerable similarities to LMN form of MND, especially because of marked fasciculations. Disorder is suspected in patients that present with asymmetrical upper limb weakness in absence of sensory disturbance. *Diagnosis* – Evidence of conduction block often between supraclavicular fossa and axilla.

Diabetic neuropathy – may be distal predominantly sensory neuropathy, neuropathy with some autonomic involvement, isolated cranial neuropathies (e.g. IIIrd nerve palsy), femoral neuropathy and a focal, predominantly motor neuropathy affecting the shoulder or lumbar plexus (diabetic amyotrophy).

Multiple myeloma. Neuropathy occurs in about 5% of patients (particularly those with disease of osteosclerotic type) and is usually of mixed sensory and motor type. Neuropathies that occur with solitary plasmacytomas often respond to radiation or removal of primary lesion.

Benign monoclonal gammopathy may be associated with demyelinating polyneuropathy. This usually has a slow course, and immunocytochemistry may show binding of IgM to, and widening of the interperiod line within myelin. Has similarity to CIDP.

Neuropathies associated with solid malignancies – *Subacute sensory neuropathy* is the most common type. It is typically associated with ataxia and may precede the detection of the tumour (usually in the lung) by several years.

Autonomic Peripheral Neuropathy

Autonomic neuropathy is the term used to describe autonomic disturbances resulting from diseases of peripheral ANS. Table 86 lists the causes of autonomic neuropathy.

Table 87 gives clinical features of autonomic disturbances in a case of autonomic neuropathy.

Investigations in Autonomic Neuropathy

- Chemistry, haematology, pathology:
  - Complete blood count
  - Blood glucose
  - HIV testing
  - Immunoelectrophoresis of blood and urine
  - Plasma norepinephrine (supine and standing)
  - Urinary porphyrin concentration
  - Genetic testing for inherited neuropathies
  - Fat aspirate, rectal or gingival biopsy for amyloid

Table 86: Causes of autonomic neuropathy

- *Immune mediated:* Acute pandysautonomia, GBS, paraneoplastic, Lambert-Eaton syn., postural orthostatic tachycardia syn., inflammatory bowel disorder related causes, chronic inflammatory demyelinating polyneuropathy.
- *Related to systemic disease:* Diabetic neuropathy, acquired amyloid neuropathy, uremic neuropathy.
- *Infections:* Botulism, HIV, Chaga's disease, diphtheria.
- *Toxic:* Alcohol, heavy metals, organic solvents, hexacarbons.
- *Drug-induced:* Vincristine, cisplatin, amiodarone, taxols, pyridoxine.
- *Hereditary:* Hereditary sensory and autonomic neuropathy (HSAN), Fabry disease, Tangier's disease, familial dysautonomia.
- *Idiopathic neuropathy:* Idiopathic distal small fibre, chronic idiopathic anhidrosis.

Table 87: Autonomic disturbances in a case of autonomic neuropathy

- *CVS:* Orthostatic hypotension, labile hypertension, brady and tachyarrhythmias.
- *GI:* Dysphagia, constipation, episodic diarrhoea, faecal incontinence, gastroparesis (persistent fullness and subsequent abdominal pain and vomiting), early satiety, abdominal bloating.
- *Urogenital:* Urinary retention or incontinence, bladder urgency, frequency, nocturia, incomplete bladder voiding, impotence, loss of ejaculation, vaginal dryness.
- *Thermoregulatory:* Hypothermia, hyperpyrexia.
- *Secretomotor:* Anhidrosis or hypohidrosis (mainly in feet), hyperhidrosis (in feet/hand/head), gustatory sweating, dryness of mouth/eyes, excessive salivation.
- *Pupillomotor:* Abnormalities of size (presents with blurred vision, difficulty in focussing, poor night vision).
- *Skin and joints:* Feeling of coldness, acrocyanosis, pallor, mottling or redness (vasomotor changes). Loss of hair, nail thickening/discoloration. Charcot's joints.

- Autoantibody assessment
  - Antinuclear antibody
  - Rheumatoid factor
  - Anti-Ro/SS-A, Anti-La/SS-B
  - Antibodies to P/Q-type calcium channel
  - Paraneoplastic antibodies
- Electrophysiological studies: Nerve conduction studies (including repetitive stimulation).
  Quantitative sensory testing.

26. ROOT AND PLEXUS SYNDROMES

RADICULOPATHY

1. **Cervical spondylosis** –

   Symptoms and signs

   (a) ***Radicular symptoms*** – due to compression of one or more nerve roots. In acute disc protrusion sudden severe pain in neck and referred in the distribution of the compressed nerve. Neck held rigid and sometimes flexed towards side of lesion. If insidious onset burning or tingling sensation sometimes accompanied by pain radiating down the upper limb. Motor symptoms usually slight or absent. Usually some diminution of appreciation of light touch and pinprick within the dermatomes corresponding to the affected radicular nerve. Tendon reflexes innervated by affected segments likely to be diminished or lost.

   (b) ***Symptoms of cord compression due to cervical myelopathy*** – Main initial symptoms are dysaesthesiae in the hands, weakness and clumsiness of the hands and spastic weakness of the lower limbs. When as is commonly the case, the cervical enlargement (C_5, C_6 and C_7) is involved, there is a combination of diminution of some tendon reflexes with exaggeration of others. The triceps jerk is most commonly diminished or lost. There may be some impairment of appreciation of light touch and pinprick over some or all the digits.

   (c) ***Pain in the neck*** – Acute disc protrusion is likely to be associated with severe pain, muscular spasm and rigidity of the neck muscles. In chronic cervical spondylosis pain is usually comparatively mild and tends to be more severe in the morning.

   (d) ***Headache*** – Characteristically occipital and often described as spreading up over the back of the head to the frontal region. Usually worse in morning.

   (e) ***Vertebrobasilar ischemia*** – Often rotation to one or other side or extension of the neck and, less frequently flexion may precipitate a brief attack of giddiness or a drop attack. Probably pressure on the vertebral arteries with consequent impairment of the blood supply of the hindbrain.

   Radiological changes – (a) Reduction of one or more disc spaces. (b) Changes in the normal curve of the spine. (c) Formation of osteophytes. (d) Sclerosis of parts of the vertebrae adjacent to the damaged discs. (e) MRI usually shows exact site of mechanical compression.

Management – (a) *Conservative* – Bed rest and analgesics in acute painful stage. Cervical collar may be used day and night to start with, and gradually let off as symptoms improve. As pain subsides active exercises for neck and shoulders combined with heat treatment. Head traction may be tried provided there are no signs of cord compression. (b) *Surgery* – When cervical movement is limited over three or four segments, laminectomy and decompression may be indicated. Anterior discectomy and fusion may be advisable in presence of excessive mobility of cervical spine.

2. **Acute cervical disc herniation** – Often associated with trauma. Posterolateral prolapse results in neck stiffness, pain and radiculopathy. In general cervical disc lesions respond rapidly to immobilization.
3. **Lesions of brachial plexus**:

   (a) ***Lesions of upper part of brachial plexus*** – Lesions are usually traumatic. Rucksack palsy is due to traction on upper part of brachial plexus from heavy rucksacs.

   (b) ***Lesions of lower part of brachial plexus***

   Thoracic outlet syndrome – In this condition, the lower trunk of the brachial plexus may be angulated over a cervical rib, together with the subclavian artery.

   Clinical features:

   Sensory – Loss in C_8-T_1 distribution.

   Motor – Wasted interossei.

   Vascular – (a) Arterial – (i) Arm claudication. Arm abduction (to 90°) and external rotation leads to reproduction of symptoms, fall in systolic BP in arm by more than 15 mm Hg, loss or diminution of radial pulse. (ii) Arm pallor, cyanosis, oedema. (iii) Supraclavicular bruit. (b) Venous – Dilated venous collaterals, axillary thrombosis.

   Investigations – (a) X-ray – of the root of the neck may reveal an enlarged transverse process or cervical rib. (b) Electromyography may demonstrate involvement of the medial cord of the plexus. (c) Doppler ultrasonic angiography to show involvement of subclavian artery, and digital subclavian to outline the vessels in more detail.

   Management – Minor symptoms can be relieved by appropriate physiotherapy, but progressive neurological deficit calls for surgical interference.

   Malignant infiltration – of brachial plexus may result from either upward extension of apical lung carcinoma, or local metastatic spread from mammary carcinoma. Pain and sensory loss in medial aspect of forearm and slowly progressive weakness which starts in the small hand muscles.

   Brachial neuralgia (Neuralgic amyotrophy) – may follow injury, operation, inoculation or specific fever. Pain is usually the first symptom, often severe and of sudden onset, followed after several days or few weeks by weakness and wasting of muscles, especially those innervated by C5 and C6 cord segments. Sensory loss is mild or absent and there are usually few or no constitutional symptoms. Recovery is slow.
4. **Fibrositis, periarthritis and arthritis of the shoulder** – Diseases of shoulder joint and its surrounding structures should be considered. Pain referred to the shoulder, to arm, or to region of elbow, associated with loss of range of movement or pain on movement.

   Treatment – None specific. In acute stage arm should be supported in a sling. Physiotherapy as soon as pain subsides.
5. **Lesions of median nerve** – Carpal tunnel syndrome (Refer).
6. **Vascular conditions** – Those producing sensory disturbances in arm include occlusion of brachial artery due to embolus, or ischemia from polyarteritis nodosa, scleroderma and other conditions grouped under the term Raynaud's phenomenon. Inspection of the skin, changes in temperature and colour of the limb, and inadequate pulse at the wrist facilitate diagnosis. Coronary insufficiency may be responsible for pain in the ulnar aspect of arm and forearm.

LUMBOSACRAL PLEXUS

Sciatica

Pain in the distribution of the sciatic nerve or its component nerve roots (L5, S1). The syndrome is now accepted as being caused by lumbar disc prolapse. However, sciatic nerve lesions can occur due to pressure in the buttock or upper part of thigh.

Causes

I. *True sciatic neuritis* – Polyarteritis nodosa, nerve injury due to injections or trauma, post-herpetic neuralgia.

II. *Mechanical pressure on nerves or roots or referred pain*–

   1. *In the spinal cord* – Tumours of cauda equina, arachnoiditis, rarely thrombosis, haemorrhage or infection irritating meninges of the cord.
   2. *In the cord space* – Protruded intervertebral disc, extramedullary tumours.

3. *In the vertebral column* – Arthritis, tuberculosis, spondylolisthesis, ankylosing spondylitis, primary bone tumours, secondary carcinoma.
4. *In the back* – Fibrositis of posterior sacral ligaments. Compression where the nerve leaves the pelvis in those who lie immobile on a hard surface for long time (a form of Saturday night palsy).
5. *In the thigh and buttock* – Fibrositis, sacrosciatic band, hip joint or sacroiliac joint disease, neurofibroma, haemorrhage within or adjacent to nerve sheath in blood dyscrasias and anticoagulant therapy, misplaced therapeutic injection.
6. *In the pelvis* – Sacroiliac arthritis or strain, hip disease, infection of prostate or female genital tract, rectal impactions, tumors of lumbosacral plexus.
7. *Lumbosacral spondylosis* is a common cause.

Investigation of a Case of Sciatica

History: Of trauma, exposure to damp or cold, sphincter control and history of previous attacks. Type of radiation whether nerve root type or vaguely localised deep aching pain. Paraesthesia will occur in pain from sensory pathways but not in referred pain. Pain down the leg on coughing in root lesions and also acute extraneural disease of spine, pelvis and sacroiliac joints.

Physical examination

1. *Lumbar spine* – Shape, mobility, muscle spasm, list to one or other side on standing (sciatic scoliosis), local tenderness and presence of trigger points in back and limbs. Sciatica may be the first symptom of spinal caries.
2. *Special signs* –
   (i) *SLR test* – Restriction of straight leg raising is usually much more marked in lesions affecting the nerve roots than in purely skeletal affections. SLR test gives a useful indication of the severity of the sciatica, and increased capacity for painless SLR is objective measure of improvement.
   (ii) *Tenderness of nerves – Tinel's sign.*
   (iii) *Intensification of pain in back and leg* during rotatory extension of lumbar spine very suggestive of ruptured disc.
   (iv) *Popliteal compression* – Radiating pain can often be aggravated by pressure over the course of the tibial nerve through the popliteal fossa. It is an additional finding in favour of root compression.
   (v) *Testing of the sacroiliac joints* – by pressure on the two anterior superior iliac spines.
   (vi) *Estimation of range and painlessness* or otherwise of hip joint by passive stretching.
   (vii) *Muscle power* in the lower limb tested against resistance.
   (viii) *Knee and ankle jerks* – When L4 root is involved knee jerk is depressed and there is likely weakness of tibialis anterior muscle. L5 root lesions, both knee and ankle jerks usually normal but there is weakness of dorsiflexion of the toes particularly of extensor hallucis longus. S1 root ankle jerk lost and weakness, when present involves the calf muscles.
   (ix) *Tone and size of gluteal muscles* judged by asking patient to contract both buttocks; in upper sacral root lesions marked wasting may be clearly visible.
3. *Sensations* – Impairment of perception of pin-prick commonly found on dorsum of foot, if implication of 5th lumbar and 1st sacral nerve roots.
4. *Presence of tender nodules* –in paraspinal muscles and along iliac crest may be found in sciatica due to inflammation of muscular and fascial structures.
5. *Rectal examination* – in older patients.

Investigations

1. *Imaging of spine* – (a) Straight X-rays – for detecting disc narrowing in lumbar spine, or lesion of sacroiliac or hip joint. (b) MRI of lumbosacral spine.
2. *CSF* – may show increased protein with normal cell count in large protruded intervertebral disc.
3. *EMG* – may be used to confirm presence of denervation in affected muscles.
4. *Procaine injection test* – for diagnosis of fibrositic pain; contact with needle aggravates local pain and elicits referred pain; procaine suppresses both, and freedom of leg and spine movement is restored.

Differential Diagnosis of Conditions Causing Sciatica

1. ***Disc lesion*** – Recurrent bouts of lower back pain (lumbago) followed by unilateral sciatica, or pain first in calf or thigh or both without any lumbar symptoms. SLR limited. Neurological signs absent, if small protrusion, present if large displacement compressing the root severely. A huge herniation may squeeze the root so hard that it becomes anaesthetic from ischemia and the pain ceases; SLR becomes once again of full range at the same time as cutaneous analgesia and loss of power and reflexes supervene.

2. ***Spondylolisthesis*** – Signs of disc lesion together with lumbar deformity. When spondylolisthesis causes intrinsic symptoms: backache after prolonged standing, or bilateral sciatica. X-ray taken with the patient standing diagnostic.
3. ***Attrition of disc*** – Full approximation of the vertebral bodies following attrition of disc allows posterior longitudinal ligament to be unduly long. Sciatica caused by standing due to compression causing posterior bulge of the disintegrated disc which is pushed back into position when posterior longitudinal ligament is taughtened by lying down. X-ray – Diminished joint space with marked anterior beaking at the affected level.
4. ***Sacroiliac arthritis*** – Alternation of pain significant, i.e., pain comes in one buttock and posterior thigh, then it transfers itself to the other side. Signs of involvement of 1st and 2nd sacral segments. No lumbar signs. Pressure on anterior iliac spines provokes pain in the buttock. SLR normal.
5. ***Secondary deposits in spine*** – Gradually increasing central backache, tendency to radiate to lower limb, soon to both. Marked limitation of movements at lumbar spine. SLR of full range though painful at the extreme. Multiradicular signs in lower limbs. Muscle weakness bilateral, unequal and marked. Spinal tenderness.
6. ***Benign spinal tumour*** – Progressive increase in symptoms. Neurological signs more severe and progressive than in disc lesion. If radiograph shows erosion of bone and induction of epidural anaesthesia does not cause disappearance of pain for the time being, a tumour is very probably present.
7. ***Major lesions in the buttock*** – such as acute osteomyelitis of ilium or upper femur, ischiorectal abscess pointing into buttock, septic gluteal bursitis. Straight leg raising and hip flexion both very painful. (In sciatica due to disc lesion hip flexion is not limited.)
8. ***Arthritis of the hip*** – Hip movements restricted and pain provoked by passive movements. Radiograph of pelvis diagnostic.
9. ***Intermittent claudication*** – When internal iliac artery is affected alone, claudication in gluteus maximus on walking may be the only symptom. Diagnostic signs – Patient lies prone and his hip is extended passively; this causes no pain. He is then asked to keep the leg extended for a minute, this brings on the claudication.

   Spinal claudication – Pins and needles in both lower limbs on walking a certain distance. All arteries of the lower limbs patent on examination. Cause is intraspinal ischemia of the nerve-roots compressed by a disc lesion or involved in arachnoiditis.
10. ***Dissecting aneurysm*** – A rare cause of sciatica is a slowly expanding aneurysm at the bifurcation of aorta compressing 3rd and 4th LNs. causing local pain and accompanied by paraesthesia and weakness in left lower limb. Severe backache. Aortography diagnostic.

Management

A. Symptomatic sciatica

1. *Acute stage* – (i) Rest in bed with boards under the mattress to support the back. (ii) Analgesics as required. (iii) Heat. (iv) Injection of 2% procaine or of lignocaine into the sciatic nerve or epidural space or tender spots in the sacroiliac region may give dramatic relief.
2. *Chronic stage* – Management will depend on cause. Conservative management – (a) High sciatica – (i) Injection of tender spots with 5% procaine. (ii) Counter-irritation, heat and massage. (iii) Epidural injection – 10 mL of 2% novocaine, followed by 80 to 100 ml. of normal saline; repeated once a week. Many patients with sciatica due to extradural adhesions may be benefited by injection of 30 mL 1% procaine hydrochloride mixed with 125 mg. hydrocortisone injected into the epidural space. Three injections are given on consecutive or alternate days. This should be followed by active and passive exercises carried out to limit of tolerance. (b) Low sciatica – Stretching of sciatic nerve, and injection of novocaine into, or as near as possible to the sheath of the nerve.

B. Sciatica due to herniated intervertebral disc

1. *Conservative treatment* – Complete rest in bed in supine position with only one pillow for 3–6 weeks. When pain is relieved, plaster jacket to immobilise the lumbar spine completely for 3–6 months. After this the jacket is removed, and a lumbar corset worn at all times during the day.
2. *Operative treatment* – Indications – (i) Acute and incapacitating symptoms not relieved by rest in bed or even immobilisation in plaster jacket. (ii) Quick recurrence of symptoms. (iii) Evidence of large prolapse causing pressure on cauda equina, or clinical evidence of severe root compressions shown by marked motor and sensory changes. Operation consists of hemilaminectomy, removal of the protrusion, and curetting out nuclear material from the central part of the disc.

C. Sciatica due to inflammation of muscular and fascial structures

Rest, local application of heat, and massage. If tender nodules, injection with 2% procaine solution. Treatment of sepsis.

Miscellaneous

Neurological aspects of pregnancy

Eclampsia – Neurological symptoms may include headache, visual disturbances, seizures and later coma. Cerebral infarction and hemorrhage may supervene. The precise pathophysiological mechanisms are poorly understood. Posterior reversible encephalopathy syndrome (PRESS).

Stroke occurs in the last trimester, but is uncommon. It is usually caused by middle cerebral artery occlusion, but occasionally results from a secondary hemorrhage caused by eclampsia. Intracranial venous thrombosis (commonly presenting with headache, seizures and focal neurological signs) occurs most commonly in the last trimester.

Peripheral nerve disorders

- Carpal tunnel syndrome often develops, possibly through fluid retention
- Bell's palsy. The incidence is about three times more than in non-pregnant women. If the condition is severe, a short course of prednisolone started within 2 days of the onset may be helpful.

Epilepsy. Frequency of seizures may increase or decrease during pregnancy, partly as a result of changes such as altered plasma protein binding, dilutional effects, changes in absorption, and sometimes poor compliance. When medication must be continued, it should be limited to monotherapy and as low a dose as possible. Folic acid 5 mg should be taken for 3 months before pregnancy and throughout the first trimester.

BENIGN INTRACRANIAL HYPERTENSION

- Iatrogenic cause
- Tetracycline
- Oral contraceptive
- Corticosteroids
- Nitrofurantoin
- Nalidixic acid
- Vit A toxicity

Pisa syndrome - Refers to axial dystonia with severe tonic lateral flexion of the trunk. Disproportionate torticollis often seen as chin on chest, whereas flexion attitude of rest of the body is normal.

Triad of normal pressure hydrocephalus

- Gait disorders
- Urinary incontinence
- Dementia

Multiple CNS defects. Causes

- Multiple sclerosis
- Multiple infarcts
- Multiple metastasis
- Meningeal carcinomatosis
- Meningovascular syphilis
- Vasculitis, e.g. PAN

Cerebral autosomal dominant arteriopathy with subcervical infarcts (ADASI) - It is a hereditary AD cause of early recurrent strokes, dementia. Migraine with atypical aura and mood disorders. The underlying lesion is widespread vaculopathy distinct from generally affecting leptomeningeal and perforating arteries of the brain. MRI shows hypertense signal in subcortical white matter and basal ganglia.

CHAPTER

8

Renal Disorders

1. INVESTIGATIONS IN RENAL DISEASE

URINE

General Characters

A. **Volume:** Varies with amount of fluids ingested, perspiration, etc. Normal average for adult 1,200–1,500 mL. (40–50 oz)

Polyuria

a. **Transient polyuria**

1. *Induced or therapeutic* (a) Ingestion of large amounts of fluids. (b) Alcohol, tea, coffee, acidifying salts like citrates or tartrates, spices, large amounts of sugar. (c) Diuretics. (d) High protein diet.
2. *Spontaneous* (a) Due to nervousness or after a nervous attack, e.g. examination, neurasthenia, after an attack of epilepsy, migraine, asthma, angina pectoris or paroxysmal tachycardia. (b) Hydronephrosis with periodic emptying of renal sac. (c) Attack of malaria, during the cold stage. (d) During convalescence from fevers like enteric. (e) Diminution or disappearance of oedema, e.g. recovery from acute nephritis, cirrhosis of liver. (f) Post-anuric diuresis. (g) Crisis of chronic nephrosis.

b. **Continued polyuria**

1. *Cranial diabetes insipidus*
2. *Nephrogenic diabetes insipidus*
3. *Primary polydipsia*

Oliguria Diarrhoea, fever, decompensated heart disease, glomerulonephritis, during accumulation of fluid in serous cavities, uraemia.

Nocturia

1. *Prostatism*
2. *Oedematous states*
3. *Polyuric states* - Diabetes mellitus/insipidus, primary polydipsia, Post-ATN.
4. *Salt-losing nephropathies* - Analgesic nephropathy, medullary sponge kidneys, sickle cell diseases.
5. *Bladder disease* - Tumour, infection (TB, fungal, schistosoma), loss of reflex inhibition (e.g. MS), vesicoureteric reflux (double micturition) in children.

B. **Transparency** – Freshly passed normal urine is clear with a faint yellow type due to urochromes.

Cloudiness - (a) Amorphous phosphates – form a white sediment in neutral or alkaline urine which disappears on addition of acid. (b) Amorphous urates – White or pink cloud which disappears on heating. (c) Blood – Bright red blood from lower urinary tract, dark red or brown from upper tract. Dipstick testing for haemoglobin is a sensitive method of detecting significant microscopic hematuria particularly when the specific gravity of urine specimen is low. (d) Bacteria – Uniform cloud or opalescence. (e) Chyluria or milky urine – due to blocking of thoracic duct by filaria or inflammatory or neoplastic conditions, with consequent rupture of lymphatics of the bladder. (f) Spermatozoa and prostatic fluid.

C. **Colour** - Depends on volume of urine voided and varies roughly with specific gravity. (1) *Colourless* – in polyuria and diabetes insipidus. (2) *Dark colour* – concentration as in fevers. (3) *Dark yellow* – bile, riboflavin, carotene containing foods. (4) *Red* – Drugs: (a) Excretion products – Rifampicin, metronidazole, sulphasalazine, doxorubicin, desferrioxamine. (b) Drug toxicity – Barbiturates (acute intermittent porphyria), clofibrate, heroin (rhabdomyolysis), warfarin, urokinase (hematuria) (ii) Beeturia. (iii) Favism. (5) *Red brown* – Urates, porphyria, myoglobinuria. (6) *Dark brown to black* – Alkaptonuria, tyrinosis, melanosis. (7) *Green to greenish blue* – Methylene blue, Ps. aeruginosa infection, indigo compounds. (8) *Cloudy* –Leucocytes, bacteria, urates (acid urine), oxalates (alkaline urine), (9) *Smoky* – Trace of erythrocytes. (10) *Bloody* – Frank hematuria.

D. **Odor** – Characteristic "aromatic" odour most marked in concentrated urine. Odour becomes *ammoniacal* during decomposition; a cloudy urine with an ammoniacal odour suggests cystitis or pyelitis, usually with obstruction in the urinary tract. Fruity odour in diabetes. Urine containing cystine may develop odour of sulphuretted hydrogen during decomposition. Articles of diet and drugs impart peculiar odour, e.g. asparagus and turpentine.

E. **Reaction** – of fresh urine usually acidic (blue litmus paper turns red) with an average pH about 6.0. pH paper range is from 4.5 to 7.

F. **Specific gravity** – Generally varies with quantity of urine. Normal range 1.017 to 1.020. Diseased kidneys lose partially or completely their ability to respond to the need of the body with the result that the urine has about the same specific gravity throughout the day (isosthenuria).

Chemical Examination

1. **Proteins** – Urine may contain mostly albumin (*selective proteinuria*) or may contain larger molecules as well (*non-selective proteinuria*). Excretion mainly of albumin signifies a glomerular lesion.

Causes of Proteinuria

1. **Physiological** – Amount of protein excreted is small and the condition is temporary. (a) Orthostatic benign – usually in older children and adolescence. (i) Urine sample passed on waking is negative for proteinuria while urine passed after 2 hours ambulation is positive. Usually increased by exercise. (ii) Proteinuria 'tubular' in character i.e. it contains small molecular weight proteins which normally pass through the glomerulus and are reabsorbed by the proximal tubule. (iii) <1 g/day. No increase with time. (b) Prolonged exposure to cold. (c) After a meal rich in proteins (alimentary proteinuria). (d) Pregnancy. (e) Pre-menstrual. (f) During first 10 days after birth.
2. **Pathological**
   a. *Glomerular lesion* – (i) Primary glomerular disease – Minimal change disease, mesangial proliferative GN, focal and segmental GN, membranous GN, mesangiocapillary GN, crescentic GN. (ii) Secondary glomerular disease – Diabetes, collagen vascular disease, amyloidosis, drugs (gold, penicillamine, mercury).
   b. *Overflow proteinuria* – Multiple myeloma, amyloidosis, myoglobinuria, haemoglobinuria.
   c. *Tissue proteinuria* – Acute inflammation of urinary tract.

Quantitative analysis of proteinuria

The following types of proteinuria are distinguished by mg of protein measured during a 24-hour urine collection:

Microalbuminuria	30–300 mg
Mild	150–500 mg
Moderate	500–1000 mg
Heavy	1000–3000 mg
Macroalbuminuria	300–3500 mg
Nephrotic range	3500 mg

Detection of protein in urine is done with either dipstick method or by using sulofosalicylic acid or trichloroacetic acid. Dipstick method is easy to perform but detects only albumin, so proteinuria not due to albumin can be missed like Bence-Jones protein in multiple myeloma.

Quantification of albuminuria can be done with 24 hour urine collection (mg/24 hr) which is cumbersome or albumin-creatinine ratio on spot urine sample which is equally reliable with range of values same as 24-hour urine collection (mg/24 hr) but measured in (mg/g)

Microalbuminuria is defined as the excretion of 30–300 mg albumin/day. Because the albumin particle is relatively small, it is often among the first proteins to enter the urine after the kidney is damaged. Screening for and monitoring the level of albuminuria has been shown to be of importance in the following conditions:

- Diabetes mellitus
- Hypertension
- Myocardial infarction
- Stroke
- Pregnancy

Systemic diseases that may present as asymptomatic albuminuria – Diabetes mellitus, amyloidosis, hypertension, gout, SLE.

Mucin – Traces in normal urine. Increased amounts in irritation and inflammation of urinary tract or vagina.

Bence-Jones protein – may be found in multiple myeloma, chronic leukaemia, osteomalacia. It precipitates on warming the urine to 40° to 60°C but dissolves almost completely when the temperature is increased to 100°C.

Principal solutes in normal urine

Organic	**Concentration (g)**
Urea	25
Creatinine	1.5
Uric acid	0.8
Hippuric acid	0.7
Indican	0.01
Ketone bodies	0.04

Other substances	2.9
Inorganic	
Sodium chloride	15
Potassium	3.3
Magnesium	0.1
Calcium	0.3
Sulphate	2.5
Phosphate	2.5
Ammonium	0.7

2. **Sugars** – *Glycosuria without hyperglycaemia* – Renal glycosuria, alimentary glycosuria after ingestion of considerable amounts of carbohydrate, glycosuria of pregnancy. *Glycosuria with hyperglycaemia* – Hyperthyroidism, emotional glycosuria, increased intracranial pressure, thiazide diuretics, ether anaesthesia.

   Non-glucose sugars

   Lactose: May be present normally. It is present in lactating women.

   Fructose: in liver disorders

   Pentose: due to drug therapy or hereditary conditions

3. **Acetone bodies** (Ketonuria) – (a) Diabetes mellitus – in which normal carbohydrate catabolism is lacking. (b) Starvation in which a deficient carbohydrate diet is the cause of abnormal fat consumption.

4. **Pigments**
   a. *Bile pigments* – (i) *Bilirubin* – Detection of small amounts of bile of value as one of the earliest signs of acute viral hepatitis. Small amounts transiently in acute cholecystitis or cholelithiasis without obvious jaundice. (ii) *Urobilinogen* – Increased urobilinogen is found in haemolytic anaemia and liver cell dysfunction.
   b. *Haemoglobin* – Haemoglobinuria occurs in extensive burns, poisoning by mushrooms and potassium chlorate, blackwater fever, symptomatic haemolytic anaemias, and paroxysmal haemoglobinurias.
   c. *Haemosiderin* – Dark yellow pigment containing iron, occurs in haemochromatosis and pernicious anaemia.
   d. *Porphyrin* – in congenital or acquired porphyrinuria.
   e. *Melanin* – in most cases of melanotic tumours.
   f. *Alkapton bodies* – In alkaptonuria, urine turns reddish brown to brownish black on standing and strongly reduces copper.

5. **Drugs** – Most poisons are eliminated in urine and their detection is useful in toxicology, e.g. lead, mercury, quinine.

6. **Myoglobinuria** – *Causes* – (a) Muscle crush injury. (b) Malignant hyperthermia. (c) Polymyositis. (d) McArdle's syndrome. (e) Acute alcoholic intoxication. (f) Heroin. (g) Rare diseases – Meyer-Betz. *Diagnosis* – (a) Acute oliguric renal failure. (b) Initial severe hypoglycaemia followed by rebound hypercalcaemia. (c) Red urine. (d) No red cells on microscopy. (e) Raised serum potassium, phosphate, urate.

2. Microscopic Examination

Crystals

In acid urine

Uric acid – Rosette-like clusters of prism and whet stone and rhombic plates. Of no significance unless in fresh urine. Their presence suggests stone in kidney or bladder or abnormal uric acid metabolism as in gout.

Amorphous urates – common in fevers. Fine yellowish or colourless granules or rarely slender prisms.

Calcium oxalate – "Envelope" crystals. Causes – Ingestion of vegetables rich in oxalic acids, such as tomatoes, spinach, asparagus and rhubarb; digestive disturbance with fermentation of carbohydrates, neurasthenia. Their presence in fresh urine, especially if they are clumped in small masses, is suspicious of calculi.

Leucine and tyrosine – indicate autolysis of tissue proteins. Clinically most frequent in acute yellow atrophy or phosphorous poisoning.

Cystine – Colourless refractile hexagonal plates with well-defined edges. Traces in normal urine. Cystinuria is due to obscure abnormality of protein metabolism and strongly predisposes to renal or cystine calculi.

Sulphonamides – Crystal forms of certain derivatives of sulphonamide may precipitate out from the urine.

Fat globules – After ingestion of large quantities of cod liver oil or other fats, phosphorus poisoning.

In alkaline urine

Phosphates – Amorphous phosphates, triple phosphates in osteitis fibrosa cystica, administration of parathyroid hormone, alkalosis, compensatory measure in acidosis to help maintain acid base balance. Magnesium ammonium phosphate "coffin-lid" crystals.

Calcium carbonate – as amorphous granules, or rarely as colourless spheres and dumb-bells.

Ammonium biurate – "Thorn apple" crystals.

Blood

RBCs lyse on the indicator pad of the dipstick, which detects haemoglobin. False-positive results occur in haemoglobinuria and myoglobinuria and may occur in

presence of oxidizing agents or large number of bacteria in the urine. Also in patients who ingest large amounts of vitamin C.

RBCs – On microscopy, glomerular and non-glomerular RBCs may be distinguished in fresh urine sample. Glomerular RBCs vary in size and shape and are often crenated in appearance; non-glomerular RBCs are uniformly round. When RBCs occur with significant proteinuria, they can be attributed to a renal rather than lower urinary tract source.

Leucocytes

Normally, 2 or 3 pus cells are present per HPF. If more than 5, it indicates urinary infection or noninfective conditions such as fever, stress, dehydration, urethral or bladder irritation.

Casts

Casts are cylinders of material that have been extruded from the renal tubule.

- Hyaline casts contain physiologically secreted tubular proteins and are not pathological.
- Granular casts indicate renal disease but are nonspecific, they are common in acute tubular necrosis.
- Casts comprising RBCs indicate significant glomerular inflammation and bleeding, they must be distinguished from granular casts with a few adherent RBCs on the surface.
- Waxy–Advanced stages of glomerulonephritis and renal amyloid disease.
- Malignant cells – may be visible as syncytia with prominent nuclei in stained filter preparations.
- "Telescoped urinary sediment" – Presence of more than 2 types of casts in a single urinary specimen together with leucocytes and erythrocytes usually implies lupus nephritis.

'Telescoped' urinary sediment

(Red cells, white cells, casts, tubular epithelial cells, fat globules) occur in collagen vascular disease especially SLE and PAN.

- WBC cast is seen in interstitial nephritis, pyelonephritis and allograft rejection.
- Eosinophiluria is seen allergic interstitial nephritis, atheroembolic disease.
- Renal tubular epithelial cells and cast is seen in acute tubular necrosis and tubulointerstitial nephritis.

Bacteriological Examination

Bacteria – most commonly found are E. coli, Pseudomonas pyocyaneus, Staphylococcus aureus, Proteus vulgaris, Klebsiella pneumoniae and Streptococcus faecalis. A clear relationship has been demonstrated between in vitro sensitivity of the organism and the outcome of treatment, and laboratory control of chemotherapy improves the chances of successful treatment.

Spirochetes – Leptospira icterohaemorrhagica.

Ova and parasites – Trichomonas vaginalis and ova of Oxyuris vermicularis and of Schistosoma haematobium. Larvae of filaria.Scolices and hooklets of hydatid cysts.

Spermatozoa – sometimes found following nocturnal emissions, convulsions or prostatic massage.

Special

Pregnancy test – Concentration of human chorionic gonadotrophin (HCG) increased (1–5 IU/mL) within one week after the first missed period.

Urinary free cortisol, catecholamines, etc.

ASSESSMENT OF RENAL FUNCTION

Indications

1. *Renal disease* – (a) Detection. (b) Evaluating its severity. (c) Following its progress. 2. *Evaluation of safety and effectiveness of drugs excreted by the kidneys.*

Tests and interpretation of results

I. **Urine examination** and usually a quantitative measurement of proteinuria.
II. **Glomerular filtration rate (GFR)** is the most widely used test of renal function.

Normal GFR is about 130 mL/minute (180 litres/day, or 2 mL/second)

Measurement of Clearance

Concept of 'clearance' – The renal excretion of any substance per unit time is equivalent to its urinary concentration (U) multiplied by the volume of urine produced per unit time (V). The rate of renal excretion must equal that of removal of solute from the blood, which may be expressed as P × C, P (plasma concentration) and C (clearance) is the virtual volume of blood that is completely cleared by the kidney of solute per unit time termed the 'renal clearance'. Thus, UV = PC, and C = UV/P.

Following filtration, water and solutes are variably reabsorbed and secreted in the tubules. Hence, tubular function, as well as glomerular filtration governs excretion, but GFR can be estimated measuring the clearance of a solute that is filtered but neither secreted nor reabsorbed in the tubule, Inulin has this property so used for estimation for

GFR. Urea and creatinine are used as surrogate measures of renal function. However, urea undergoes passive tubular reabsorption and creatinine is actively secreted in the proximal tubule; hence urea clearance underestimates GFR and creatinine reabsorption clearance overestimates it.

Inulin clearance – involves infusion of inulin to produce a steady-state concentration; urinary excretion, which requires accurately timed urine collection, is then measured, allowing calculation of inulin clearance. Alternatively, a single bolus injection of inulin followed by sequential measurements of its disappearance from the plasma may be used. The method is now seldom performed.

Other Clearance Methods

Isotope methods – A single bolus injection of ^{51}Cr-EDTA with subsequent blood sampling. Disadvantages include radiation exposure and high cost.

Dynamic renography – An estimate of GFR can be obtained from a dynamic renogram (^{99}Tc-DPTA or ^{99}Tc-MAG3), but this method is less accurate than EDTA unless it is combined with blood sampling.

Iohexol – A low osmolality, non-ionic contrast medium is non-radioactive and can be measured by high performance liquid chromatography. Iohexol clearance is a simple, reliable and accurate method of estimating GFR.

Table 1: Causes of abnormal creatinine and urea in blood

Creatinine
Raised
• Large muscle bulk
• Acute rhabdomyolysis
• Reduced tubular secretion (trimethoprim, potassium-sparing diuretics, probenecid, triamterene)
Reduced
• Small muscle mass
• Pregnancy
• Raised antidiuretic hormone
Urea
Raised
• Reduced GFR (including dehydration)
• GI bleeding
• Corticosteroids/tetracycline
• Catabolic state
• High-protein diet
Reduced
• Liver disease
• Starvation/anabolic state
• Pregnancy
• Raised antidiuretic state

Cystatin C is an endogenous cysteine protease inhibitor. It is a low molecular weight protein that is freely filtered by the glomerulus and is produced at a relatively constant rate. Its levels are independent of tubular function, and are therefore closely related with GFR.

Creatinine clearance – Creatinine production is relatively stable and therefore creatinine clearance is commonly used as an estimate of GFR. Urine collection should begin on an empty bladder. Patient should note the time and collect all the urine in next 24 hours, ending with complete emptying of the bladder at the same time on the following day.

Creatinine clearance gives a good approximation of glomerular filtration at high GFR. At lower GFR, however the contribution from tubular secretion becomes more important and creatinine clearance tends to overestimate GFR by 10–20%. In addition some creatinine is lost through the bowel. Patients with creatinine clearance < 15 ml/minute must be considered for dialysis.

Estimation of creatinine clearance (Cockroft-Gault equation)

Men

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times (\text{wt. in kg})}{72 \times \text{Serum creatinine (mg/dL)}}$$

Women: For women, above formula is multiplied by 0.85

Note: The formula should not be used in patients below age or 18 years, those grossly obese, oedematous or cachectic, or with ascites, or when muscle mass is reduced (e.g. paraplegias), or in pregnant women.

Serum urea and creatinine concentrations – are the simplest monitors of renal function. The level of urea or creatinine depends not only on the glomerular filtration but also on the rate of production of the solute (Table 1).

At times, there may be certain substances in blood that interfere with creatinine measurement (Table 2).

Reciprocal creatinine plots – A single measure of plasma glomerular filtration does not provide a reliable indicator of GFR. However, the rate of production of

Table 2: Substances that interfere with creatinine measurement

Endogenous substances	*Common drugs*
Protein	Cephalosporins
Ketones	5-fluorocytosine
Glucose	Methanol
Bilirubin	Metabolites
Fatty acids	
Urate	
Urea	

creatinine is more constant than that of urea. There is a relationship between creatinine and GFR, by which creatinine is proportional to the reciprocal of creatinine clearance (P = UV/C). At high levels of GFR, even large changes in renal function can lead to minor alterations in serum creatinine. Conversely, at low levels of GFR a large change in creatinine can arise from small changes in renal function.

In many forms of CRF, decrease in GFR occurs at a constant rate, and a plot of the reciprocal creatinine level against time should therefore give a straight line. Any deviation from the predicted plot may give an early indication of an intercurrent additional renal insult.

Cystatin C is a biomarker for kidney function. If kidney function and GFR decreases, cystatin C level rises. It is a better test for kidney function than creatinine (Table 3). Cystatin C levels are altered in patients with cancer, impaired thyroid function

Differential renal function – In some situations (particularly when planning surgery), it is important to know the relative contribution of each kidney to overall renal function. This can be determined using ^{99}Tc-DMSA, which localizes in the proximal tubular cells. Using a gamma camera, activity-time curves are generated for each kidney. Uptake of activity by each kidney can then be used to determine the relative contribution to overall GFR. The error with this technique lies in the difference in depth of the two kidneys; each 1 cm difference accounts for a 10% difference in activity count.

TESTS OF TUBULAR FUNCTION

1. **Urinary concentration and dilution** – Inability to concentrate the urine to more than 600 mOsmol/litre indicates diabetes insipidus. Cranial diabetes insipidus can be distinguished from nephrogenic diabetes insipidus by subsequent response to ADH.

   The ability to dilute urine to achieve maximum free water clearance is also often impaired in patients with CRF. It can be assessed by administering 1000–1500 mL water (12 mL/kg body wt). More than 75% of the water load should be excreted within 3 hours and urinary osmolality fall below 100 mOsmol/kg.

Table 3: Cystatin C levels and GFR

Cystatin C level	*Interpretation*
0.5–6.9	Normal GFR
1–1.2	Mild decrease
1.3–1.9	Moderate decrease
2–3	Severe decrease
> 3.5	End-stage kidney disease

2. **Urinary acidification tests** – In distal type I and type II renal tubular acidosis (RTA), patients are unable to generate an acid urine (pH<5.5). Diagnosis is confirmed if low urine pH is not achieved in presence of systemic acidosis. Oral acidification tests (usually with ammonium chloride) are indicated only in partial RTA, in which patients are hypocalcaemia but not acidotic as a result of increased excretion of hydrogen ions with ammonia. In the proximal type II RTA, bicarbonate resorption is defective; the urine may still be acidic if bicarbonate entry to the tubule is reduced by severe systemic acidosis and/or low GFR.
3. **Urinary electrolytes and other tests of tubular function** – Measurement of 24-hour sodium output is at times helpful in managing patients with salt-losing nephropathy. Low urinary sodium (< 10 mm) is associated with prerenal failure but this measurement should not determine management because a higher sodium level will not respond to appropriate filling. Tests of proximal tubular function may be required in the investigation of Fanconi's syndrome or isolated proximal tubular defects (e.g. urate clearance). Bicarbonate, glucose, phosphate and amino acids are normally reabsorbed in the proximal tubule, their presence in the urine is abnormal.

RENAL IMAGING

Ultrasonography – has largely replaced IVU as the first-line investigation of renal disease. The bladder should be imaged full, to allow optimal assessment of wall thickness, masses and calculi. Post-micturition volume can be assessed. Indications for renal system ultrasonography are given in Table 4.

Doppler ultrasonography – Using colour Doppler, vessel patency, direction of flow and abnormal vascularity can be determined.

Plain abdominal radiography – of kidneys, ureters and bladder (KUB). Renal outline can be defined, calcification may be detected in renal areas, ureters, bladder and urethra. Common causes of renal tract calcificationare urinary calculi, and nephrocalcinosis, focal calcification (e.g. tuberculosis, tumour) is also seen.

Intravenous urography (IVU) – gives excellent anatomical information and some indication of function, but diagnostic IVU may be difficult to perform in patients with renal impairment. A 1-minute film after IV injection of contrast medium, coned to renal area, coincides with highest concentration of contrast medium in the nephrons and this 'nephrogram' can be used to assess renal size and outline. A 5-minute film shows the pelvicalyceal system,

Table 4: Indications for renal system ultrasonography

Paediatrics
• Renal masses – hydronephrosis, tumours, cystic disease
• Bladder dysfunction
Renal failure
• Obstruction – Pelvicalyceal dilatation
• Kidney size, cortical thickness and scars
Renal masses
• Differentiation of simple cystic and solid lesions and abscesses
• Tumour extension into renal vein
Calculi
• Detection of radiolucent stones
• Demonstration of site of stone impaction
Renal transplantation
• Complications – obstruction and vascular patency, perirenal collections (e.g. lymphocoele, urinoma)
Bladder
• Post-micturition volume combined with flow rate
Renal Doppler
• Renal artery stenosis
• Venous patency
• Vascularity of renal masses
Intervention
• Renal biopsy
• Nephrostomy
• Cyst aspiration
• Drain insertion
Prostate
• Transrectal ultrasonography
• Prostatic biopsy

detecting abnormal filling defects. Further films show ureters and bladder. A post-micturition film is looked at for bladder emptying, intravesical abnormalities and obstruction. The IVU films series should be inspected for:

Kidneys

- Kidney length is about 3 lumbar vertebrae. The left kidney is slightly higher and larger than the left.
- Renal outline should be smooth. Patients with renal masses may have associated calyceal distortion.
- Calyceal dilatation may be caused by obstruction or by disease of the papilla (papillary necrosis, pyelonephritis, reflux nephropathy).
- The renal pelves are inspected for filling defects (e.g. tumour, stones, blood clot, sloughed papilla).

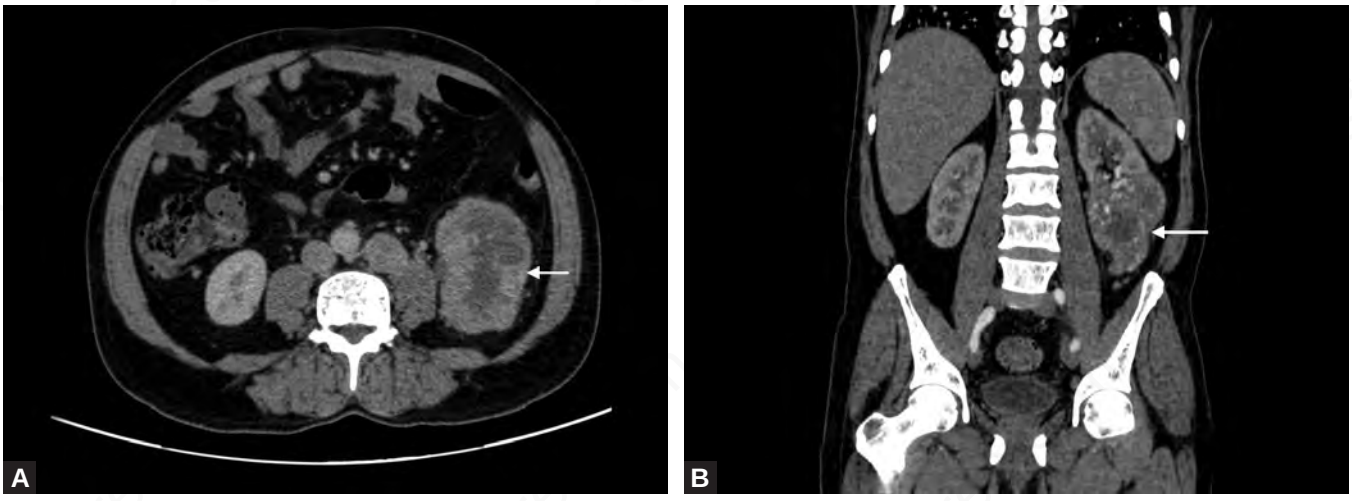
Ureters – Opacification of the whole ureter suggests distal obstruction. Displacement occurs in retroperitoneal pathology (e.g. retroperitoneal fibrosis).

Bladder – Contour should be smooth and no post-micturition residual volume should be seen.

CT – provides excellent anatomical and functional information on renal perfusion and filtration. Using fast spiral CT, kidneys can be imaged initially in the parenchymal phase, followed by the pyelogram phase (analogous to IVU).

Indications

- Renal trauma
- Staging and assessing response to therapy in renal (Figs. 1A and B), bladder (Fig. 2), prostatic and testicular carcinoma
- Investigation of renal masses when ultrasonography is equivocal or tumour is small



Figs. 1A and B: CECT (A) axial and (B) coronal image showing left renal mass at lower pole (arrow)

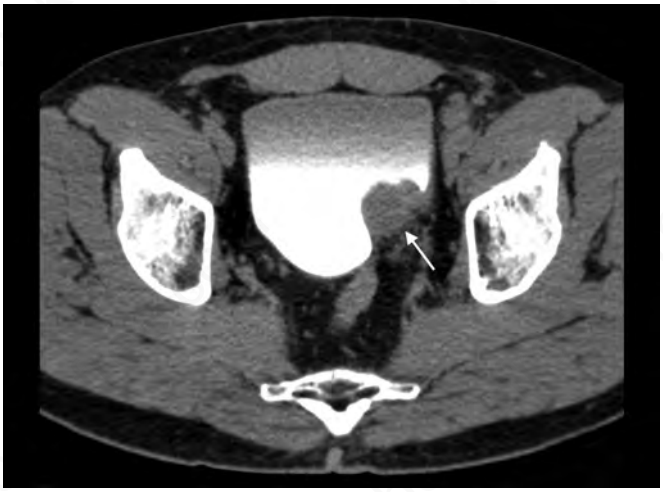


Fig. 2: CECT showing carcinoma of bladder (arrow)

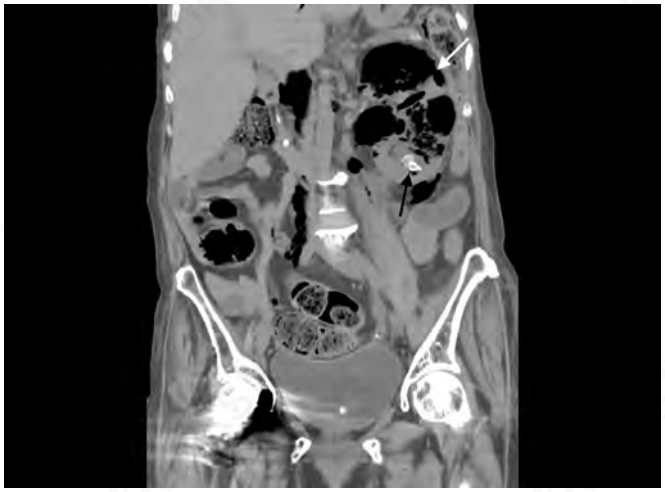


Fig. 3: CT coronal view showing left renal calculus (black arrow) with emphysematous pyelonephritis (white arrow)

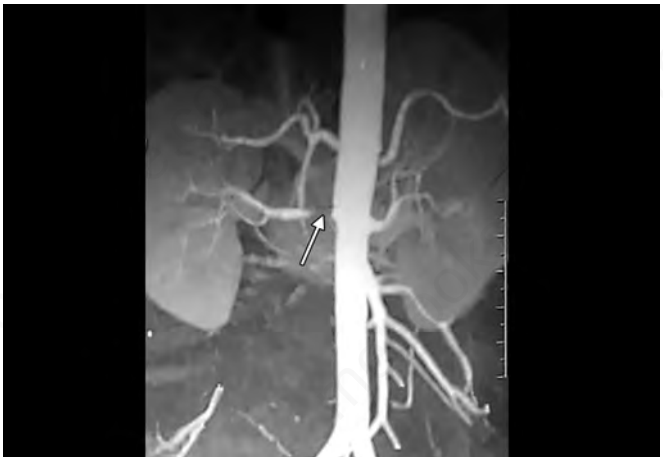


Fig. 4: Angiography showing right renal artery stenosis (arrow)

- To distinguish stones (Fig. 3) from transitional cell carcinomas when a pelvicalyceal defect is seen on IVU or ultrasonography
- Detection of ureteric calculi
- Retroperitoneal fibrosis and masses

Spiral CT angiography demonstrates the renal vasculature, this is useful in renal artery stenosis (Fig. 4), and shows the relationship of renal arteries to aortic aneurysms.

MRI – is used principally in the staging of pelvic, prostatic and renal tumours, as an alternative to CT. Renal cell carcinoma, angiomyolipoma and simple and complex cysts can be readily distinguished by MRI, which is an excellent means of imaging thrombus, tumour in the renal veins. It is useful in those who are intolerant of iodinated agents because of allergy or nephrotoxicity and in pregnancy.

Magnetic resonance urography (MRU) is used in patients with chronic urolithiasis or ureteric tumour, and in paediatric uroradiology. It can be performed in two ways:

- Excretory MRU is analogous to IVU.
- In static-fluid MRU, non-enhanced T_2-weighted sequences produce excellent images of markedly dilated urinary tract, even in patients with markedly impaired renal function.

Magnetic resonance angiography is the most common form of renal MRI. The renal artery can be studied with or without contrast, though the use of IV gadolinium considerably improves sensitivity and specificity. The sensitivity is comparable to that of angiography or multislice CT in determination of renal artery stenosis.

Interventional magnetic resonance procedures– Open- access scanners can be used to perform nephrostomy and take biopsies.

Nuclear medicine

Static renal scanning uses ^{99}mTcdimercapto-succinic acid (^{99}mTc-DMSA), which binds to the proximal renal tubules. The kidneys are imaged 3 hours post-injection, when about 15% of the tracer has been excreted. About 20% is retained in each kidney. It is used mainly in children to identify renal scarring.

Dynamic renography uses radiolabelled tracers that are excreted rapidly by the kidneys, their arrival, uptake and elimination are imaged using a gamma-camera.

Uses

1. Venography gives useful information on degree of obstruction, relative renal function and renal artery stenosis.
2. Assessment of renal transplants, in terms of perfusion, filtration and drainage.
3. In obstruction, frusemide may be given IV at 15 minutes post-tracer injection and the amount of washout calculated; this is useful to confirm pelviureteric junction obstruction.
4. In children vesicoureteric reflux (indirect radionuclide cystography) should be sought during micturition. In significant renal artery stenosis, tracer uptake is decreased after administration of captopril, reflecting reduced blood flow and renal function.

Direct radionuclide cystography – ^{99m}Tc is instilled to maximum bladder capacity. The kidneys and ureters are imaged continually during this procedure and subsequent micturition views are assessed for reflux.

Special techniques

Ureterography is used to identify urethral strictures or injuries in men.

Micturating cystography – Contrast medium introduced via a catheter fills the bladder to capacity; the catheter is removed and films are taken during voiding with the patient upright using fluoroscopy. It is used to look for vesicoureteric reflux, structural bladder and urethral abnormalities (urethral valves, bladder diverticula) and micturition dysfunction.

Antegrade pyelography is used to identify the precise level in upper renal tract. A needle is inserted into a dilated pelvicalyceal system under ultrasound or fluoroscopic guidance. The initial urine sample is sent for culture and cytology. Contrast medium is then used to opacify the urinary tract and identify the level of obstruction. This can be undertaken as a prelude to nephrostomy.

Retrograde pyelography is now seldom performed but is indicated in suspected transitional cell carcinoma of the upper renal tract. The ureters are catheterised retrograde and contrast is introduced to opacify the upper tracts.

Angiography – Its use has declined since the introduction of CT and ultrasonography. It is usually performed using DSA.

Indications –

1. In live transplant donors to document the number and pattern of renal arteries and to confirm the normality of the other kidney.
2. As a part of embolization procedure for AV malformations, in fistulas and as palliative embolization therapy for renal tumours.
3. As a diagnostic and therapeutic tool in renal vascular abnormalities such as renal artery stenosis and fibromuscular dysplasia, and angioplasty can be performed at the same time.

Venography can be performed to demonstrate renal venous patency as part of varicocoele embolization and detection of undescended testis.

Interventional uroradiology – Nephrostomy (insertion of a catheter into the pelvicalyceal system) is a common urinary tract intervention. It is indicated in obstruction to prevent loss of renal function, in presence of pyonephrosis and for pain relief. Percutaneous nephrolithotomy may be performed to extract calculi from renal pelvis. Other procedures that can be performed subcutaneously include biopsy, pyelolysis in PUJ obstruction, ureterolithotomy, antegrade stent insertion, and cyst and abscess aspiration.

KIDNEY BIOPSY

Indications

1. ***Asymptomatic proteinuria*** – Patients with normal renal function but persistent proteinuria of 2 g or more/24 hrs. Biopsy may demonstrate a treatable condition such as SLE, membranous nephropathy.
2. ***Nephrotic syndrome*** – (Proteinuria >3 g/24 hours, plasma albumin <35 g/litre and oedema) in patients under 1 year or over 10 years of age require renal biopsy. In 1–5 years old, likelihood of minimal change nephropathy is more than 90%; this responds to corticosteroid treatment. Therapeutic trials of high dose corticosteroids can be avoided.
3. ***Persistent proteinuria and hematuria*** – associated with renal impairment measured by GFR.
4. ***Acute renal failure*** – The most common finding is vasculitis. This is usually seen as vasculitic GN, in which destruction of varying amounts of the glomerular tuft occurs in varying numbers of glomeruli. Other common findings are acute interstitial nephritis, small vessel vasculopathy of the type seen in scleroderma, accelerated hypertension or haemolytic uraemic syndrome, myeloma kidney and acute post-infective GN.

   In all these causes of ARF, the tubules are abnormal and acutely damaged. If acute tubular damage is the only finding, it suggests a likely cause (e.g. the effects of gentamicin).

5. ***Chronic kidney failure with normal-sized kidneys*** – An accurate histological diagnosis may help determine prognosis and plan treatment. Biopsy may be useful in diagnosis of paraprotein-associated disease, in which the outlook for the patient may be limited, and focal segmental glomerulosclerosis, in which transplantation is associated with a significant risk of disease recurrence.
6. ***Renal allograft dysfunction*** – Biopsy is used to determine whether an immune response against the transplanted kidney (rejection) is present. Acute rejection occurs soon after transplantation and often takes the form of acute cellular rejection. Acute vascular rejection is less common. Many grafts develop slow narrowing of the arteries leading to ischaemia, loss of tubules and decline in function (chronic vascular rejection).
7. ***Systemic disorders*** – Associated with hematuria, proteinuria or impaired renal function. Biopsy important for determining diagnosis and prognosis. Severity of renal lesion may influence nature of therapy, e.g. in SLE, serial biopsies may be useful in judging response to treatment.

Contraindications

1. Single kidney or severe malfunction of one kidney.
2. Uncontrollable bleeding diathesis.
3. Small, shrunken kidneys (difficult to locate, and information obtained usually non-specific).
4. Asymmetrical kidneys with significant discrepancy in split function (measured by isotope technique).
5. Reflux nephropathy.
6. Acute urinary infection

   In patients with a coagulation defect, transjugular renal biopsy may be used.

Preparation – Investigations required are FBC, electrolytes, urea and creatinine, LFTs, clotting screen, group and store serum for blood crossmatching, and ultrasound measurement of the size and symmetry of the kidneys. Serology for anti-GM antibodies if required. Premedication and IV line. Diastolic B.P. should be controlled at less than 90 mm Hg. If creatinine is > 400 μmol/L, DDAVP may be given parenterally to reduce risk of bleeding.

Technique

Localization of the kidney – (a) *Native renal biopsy* – Lateral border of lower pole of kidney is the safest area to biopsy. Ultrasound is the preferred imaging technique to mark the position of the kidney. It is particularly preferred in patients with impaired function as it avoids use of contrast media. (b) *Allograft biopsy* – Safest area is generally the lateral border of the more accessible pole.

Biopsy needle – Disposable needles of the Tru-cut type or newer, automatic systems, in which the core of tissue is taken automatically by rapid opening and closing of the needle using a spring mechanism. Spring-loaded techniques require fewer passes to obtain tissue and allow use of finger gauge needles.

Complications – Complications of renal biopsy are listed in Table 5.

Table 5: Complications of renal biopsy

• Hematoma – Occult (visible by CT) – Clinically significant
• A-V fistula – Occult (demonstrable by angiography) – Clinically significant
• Macroscopic hematuria (Microscopic hematuria occurs in most patients)
• Blood loss requiring transfusion
• Infection
• Surgical intervention required post-biopsy
• Loss of kidney
• Inadvertent biopsy of other organs (e.g. liver, spleen, pancreas, intestine, gallbladder, adrenal glands)

2. HEMATURIA

Causes of hematuria are listed in Table 6.

Table 6: Causes of haematuria

In the urinary tract
Kidney • Congenital anomalies—Polycystic disease, angioma. • Calculus. • Mobile kidney. • Infections – Pyelonephritis, tuberculosis, glomerulonephritis. • Neoplasms – Renal carcinoma, Wilm's tumour. • Drugs – Sulphonamides, anticoagulants. • Trauma – Ruptured kidney. • Oxaluria. • Post-operative – After nephro- or pyelolithotomy or partial nephrectomy.

Contd...

Contd...

- Radiation damage.
- Hereditary nephritis – Airport's syndrome, familial recurrent haematuria.
- Renal embolization/infarction.
- Analgesic nephropathy.
- Unknown origin – Essential haematuria ("renal epistaxis"). Loin pain/haematuria syndrome.

Ureter
- Trauma.
- Calculi.
- Infection.
- Tumours – Papilloma, carcinoma.

Prostate
- Benign hypertrophy
- Carcinoma.

Bladder
- Diverticulum.
- Trauma – following prostatectomy or other operations or instrumental.
- Calculus or foreign body.
- Tuberculosis.
- Tumours – Simple, papilloma, carcinoma.
- Ulcers.
- Chemical cystitis – e.g. after cyclophosphamide.
- Parasitic – Schistosomiasis, bancroftian filariasis.

Urethra
- Malformations.
- Injuries.
- Calculus or foreign body.
- Infections.
- Tumours.
- Naevus.

Systemic causes
- Bleeding diathesis.
- Collagen disorders – SLE, PAN.
- Subacute infective endocarditis.
- Cryoglobulinaemias.
- Amyloidosis.
- Acute fevers – Malignant malaria.
- Tuberous sclerosis (associated angiomyolipomata).
- Severe exertion (e.g. jogging).

Investigation of a Case of Haematuria

History

1. *Age* – Newborn – Haemorrhagic disease due to deficiency of vitamin K. Child – Acute nephritis, acute leukaemia, acute infectious fevers, scurvy, haemophilia, bladder stone, meatal ulcer. Young adults – Renal calculus or tuberculosis, gonococcal urethritis. Middle or old age – Bladder tumours, congenital cystic kidneys, calculus, hypernephroma and other malignant tumours, hypertension, enlarged prostate.
2. *Sex* – Bladder stone almost always in males.
3. *Family history* – of polycystic kidneys or urinary calculi.
4. *Drugs* – History of taking anticoagulants, sulphonamides or large doses of aspirin.
5. *Previous history* – of pulmonary or bone and joint tuberculosis.
6. *Quantity of blood* – Profuse in tumours of kidney or bladder injury with rupture of kidney. Rarely tuberculosis and enlarged prostate.
7. *Precipitating cause* – Trauma, jolting or exercise in renal calculus. Instrumentation. Intercourse.
8. *Timing of bleeding in relation to urinary stream* – Terminal haematuria preceded by clear urine suggests source in bladder, initial haematuria followed by clear urine is indicative usually of lesion in urethra. Haematuria equally distributed throughout the urinary flow is characteristic of renal and ureteric lesions, but may occur in bleeding from the bladder.
9. *Pain* – (i) Colicky in stone. (ii) Loin pain suggests renal cause. (iii) Pain at tip of penis especially after micturition indicates irritation of trigone. (iv) Pain in perineal area – malignant disease of bladder or prostate. (v) Hypogastric pain in cystitis. (vi) In Dietl's crisis, severe pain but haematuria rare. Haematuria precedes pain in tuberculosis and new growth of kidney; follows pain in renal stone.
10. *Absence of pain* – Enlarged congested prostate, early stage of malignant disease of bladder, renal neoplasms, congenital cystic kidneys, tuberculosis and systemic causes. Painless, periodic, progressive and profuse haematuria in simple papilloma.
11. *Increased frequency of micturition* – Local causes in bladder, tuberculosis or pyelitis.
12. *Constitutional symptoms* – Fever in pyelitis and cystitis. Rash or eruption in acute fevers.
13. *Haemorrhage elsewhere in the body* – in purpura, haemophilia, fevers, hypertension.

Physical Examination

a. *Local examination*:
   1. Palpation of kidneys – (i) Unilateral tumour – in tuberculosis, hypernephroma, hydro- or pyonephrosis. (ii) Bilateral in polycystic disease.
   2. Bladder tumour is occasionally palpable.
   3. Inspection of external genitals and urinary meatus for local causes.
   4. Examination of testis and epididymis for evidence of tuberculosis.
   5. Rectal examination – Enlarged prostate, stone in bladder in children.
   6. Vaginal examination – pelvic tumour, e.g. malignancy of uterus.

b. *General examination* – Examination of heart for SBE. Blood pressure. Signs of anaemia. Bruising or other evidence of haemostatic defect. Abdominal palpation for splenomegaly, enlarged kidneys or distended bladder.

Investigations

1. *Urine* – (i) Excess of crystals of uric acid, oxalates, etc., may indicate presence of stones. (ii) Albuminuria and epithelial cells in acute nephritis. (iii) Pus cells in pyelitis and tuberculosis. (iv) Red cells – In glomerular bleeding there is great variation in size and many cells show loss of normal haemoglobin pigment. In non-glomerular bleeding the cells are uniform in appearance and usually have normal haemoglobin content (except in acid urine). (v) Renal tubular epithelial cells – A sharp rise in these cells may be produced by certain drugs. The number of these cells is greatly increased in acute tubular necrosis. (vi) Casts – Red cell casts or casts containing red cells imply glomerular disease. Granular casts, oval fat bodies and broad, waxy casts imply an underlying renal lesion. (vii) Culture – Pyuria with no growth on urine culture occurs with tuberculosis, tumours of urinary tract and analgesic nephropathy. (viii) Cytology – when urothelial neoplasm is suspected.
2. *Blood examination* – for evidence of hypoprothrombinaemia, purpura or haemophilia.
3. *Chest radiograph* – for evidence of malignancy or tuberculosis.
4. *Cystoscopy* – If IVU and urine culture are normal. Upper urinary tract bleeding is usually unilateral. Bladder tumours and pre-malignant papillomata can be diagnosed by cystoscopy, with biopsy when necessary.
5. *Renal imaging.*
6. *Additional investigations*:
   a. *Serum calcium and phosphorus* – to exclude hyperparathyroidism with urinary calculi.
   b. *Serum acid phosphatase* – Elevated in carcinoma of prostate associated with metastases.
   c. *Prostatic biopsy* – when prostatic carcinoma is suspected.
   d. *Prostatic exfoliative cytology* – Examination of prostatic fluid obtained by prostatic massage may show malignant cells.
   e. *Kidney biopsy* – in patients with recurrent haematuria in whom IVU and cystoscopy are normal and urine shows proteinuria, red cell casts and impaired renal function and raised serum IgA concentration.

3. GLOMERULAR DISEASES

A group of diverse entities, including, but not limited to glomerular inflammation (glomerulonephritis). Structural, functional and clinical similarities exist within the group because of the limited ways a tissue can respond to injury, and these injuries manifest as symptoms and signs.

Mechanism of glomerular injury – Many glomerular diseases, whether occurring in isolation or as part of multisystem diseases, are associated with demonstrable immunological abnormalities. There are two possible mechanisms:

1. ***Antigen in kidney*** – (in situ complex formation) – Antigen may be an intrinsic part of the glomerulus, or derived from other parts of the body and deposited in the glomerulus. Thus formation of antigen-antibody complex can occur if an appropriate antibody is generated.
2. ***Antigen remote from the kidney*** – (Antigen either endogenous or exogenous from other sources than the kidney) – When the antigen-antibody complex gains access to, or is produced in the circulation, it can be deposited in the kidneys, where it activates mediators of inflammation. The production of glomerular injury is complex and probably depends on linked cellular and non-cellular mechanisms. Immunohistopathological study of renal tissue from renal biopsies reveals antibody (IgG, IgM or IgA) and complement components. Also the common finding of monocytes, macrophages (producers of TNF-alpha and interleukin-1) and T helper lymphocytes (producers of interleukin-2) suggests a role for these cells and cytokines in pathogenesis.

Table 7: Causes of glomerular disease

1. Hereditary disorders –
   - Alport's syndrome – Progressive nephritis and sensorineural hearing loss. Characteristic 'basket-weave' appearance of glomerular basement membrane.
   - Thin membrane basement disease – presents as recurrent hematuria.
   - Familial clusters – Some conditions like minimal change nephropathy, focal and segmental glomerulosclerosis have been reported in familial clusters.
2. Systemic disease in which glomerulonephritis may feature
   - Connective tissue diseases, particularly SLE
   - Systemic vasculitis
   - Infective endocarditis
   - Other infections including Staph. aureus, malaria, hepatitis B, HIV
   - Drug reactions (NSAIDs, gold, penicillamine), carcinoma, lymphoma, myeloma
3. Idiopathic

CAUSES OF GLOMERULAR DISEASE

These are listed in Table 7.

PRESENTATION OF PRIMARY GLOMERULAR DISEASE

- Asymptomatic proteinuria
- Nephrotic syndrome
- Nephritic syndrome
- Microscopic hematuria (occasionally macroscopic particularly after intercurrent infections in IgA nephropathy)
- Hypertension
- Rapidly progressive glomerulonephritis

ACUTE GLOMERULONEPHRITIS

A disease most common in children, characterised pathologically by diffuse inflammatory changes in the glomeruli and clinically by usually abrupt onset of macroscopic hematuria, proteinuria (usually moderate), oedema, hypertension and impaired kidney function with or without oliguria. Not all features may be present at the same time.

Pathogenesis of GN – Immune reactions underlying GN: There are contributions from cellular immunity (T lymphocytes, macrophages), humoral immunity (antibodies, immune complexes, complement), and other inflammatory mediators (including the coagulation cascade). In some cases, the target of immune response is known (e.g. when GN complicates infections or tumour). In many cases, the target is unknown and an autoimmune aetiology is suspected.

As in other autoimmune conditions, primary GN is considered to result from an interaction between genetic susceptibility and an environmental precipitant. Genetic factors are typically genes involved in control of the immune response, particularly major histocompatibility complex and HLA genes. Environmental precipitant may be drugs, chemicals or infectious agents. The role of immune mechanisms in the pathogenesis of GN is indicated by the presence of circulating autoantibodies and/or abnormalities of serum complement, and glomerular deposition of antibodies, immune complexes, complement and fibrin.

Clinical Features

Modes of onset – (a) Oedema – puffiness of face. (b) Urinary symptoms – Scanty and smoky or frank bloody urine. (c) Symptoms of acute infection – Fever, bodyache, vomiting. (d) Cerebral symptoms – Headache, convulsions. (e) Insidious onset – Weakness, pallor, loss of appetite. (f) Accidental discovery – on routine urine examination.

Symptoms and Signs

1. *Oedema* – may come on suddenly or gradually. Puffiness of face and whitish pallor constitute "nephritic facies", swelling of face usually in morning. Generalized anasarca may occur. Oedema may be absent in mild cases and also in very severe cases.
2. *Hypertension* – occurs in majority ofcases, the diastolic pressure being 90 to 120 mm usually, and as a rule persists for at least one week, returning to normal a few days after patient has had diuresis. In 5 to 10% cent cases hypertensive encephalopathy develops. The rise of pressure may give rise to pulmonary oedema. JVP is commonly elevated and with peripheral oedema presents a picture of CHF. Renal retention of salt and water is responsible for the circulatory disturbance.
3. *Impaired renal function* – Oliguria. Acute renal failure develops in some.

Laboratory Tests

1. *Urine* – Volume reduced, dark in colouror smoky when fresh, tea-coloured afterhaemolysis. Proteinuria variable, rarely more than 2.5 g per day. Red cells and red cell casts. Also white cells, white cells casts and granular casts.

2. *Evidence of streptococcal infection* – in post streptococcal GN. Demonstration of presence of A beta-haemolytic streptococcus of nephritogenic M - protein type in throat or skin lesion, and of an immune response to one or more of streptococcal exoenzymes.
3. *Haematology* – Polymorphonuclear leucocytosis, raised ESR.
4. *Osmolality* – of diagnostic help because osmolality of urine is often appreciably higher than that of plasma in acute nephritis in contrast to other forms of acute renal failure.
5. *Renal biopsy* – Indications – (i) Unusually protracted course, especially if accompanied by kidney failure. (ii) Suspicion of multisystem disease. (iii) Transition to nephrotic phase. (iv) Persistent hypocomplementaemia.

Tests to Exclude a Systemic Disorder Underlying GN

- Chest radiography (plus more detailed screening for malignancy if suspected)
- Microbiological tests (e.g. blood culture, viral serology)
- Lupus serology (particularly anti-DNA antibodies)
- Serum complement levels (low C3 and/or C4 common in acute lupus, systemic infections, immune complex disease)
- Antineutrophil cytoplasmic antibody (if systemic vasculitis is suspected)
- Myeloma screen (serum immunoglobulin electrophoresis urine test for Bence-Jones protein)

Course – Complete recovery occurs in majority of children and in about 50 % of adults. Even when acute renal failure develops the patient may recover despite oliguria lasting for several weeks. Haematuria, which is often exacerbated by exertion, commonly persists for 6–12 months before complete recovery. Slight proteinuria persists for many months before returning to normal.

Complications – (a) Acute renal failure. (b) Acute heart failure with pulmonary oedema. (c) Hypertensive encephalopathy. (d) Urinary tract infection especially if oliguria is prolonged. (e) Renal or urinary tract pain occasionally as a result of clot colic. (f) Arthritis occurs rarely and suggests multisystem disease.

Management

1. *Rest in bed* – diminishes risk of pulmonary oedema and hypertensive crises. In a mild case, 3 weeks, in more severe cases it must at least be 3 months. Persistence of microscopic haematuria, or proteinuria under 1 g day does not justify prolonged bed rest. Patient should be allowed to be up and about once urinary findings have become stationary. Bowels should be kept open.
2. *Restricted fluids* – (Fruit juices contain potassium and should be used with caution in oliguric patients). First 24–28 hours only 500 mL of water and glucose or barley water. After that if urine volume in 24 hours is less than 400 mL, treat as for acute renal failure. If urine volume is more than 400 mL limit intake of fluid to 500 mL plus a volume equal to that passed in preceding 24 hours; low salt, low protein diet can be started.
3. *Diet* – Low protein diet. If patient is oedematous or has engorged neck veins, the diet should contain very little sodium.
4. *Antibiotics* – Benzathine penicillin G 500,000 units IM 6-hourly to destroy any residual haemolytic streptococci. Erythromycin 250 mg qds if penicillin is not tolerated.
5. *Management of complications* – (i) Convulsions – IV Diazepam 10 mg slowly, if fits recur phenytoin sodium 100 mg bd IM (ii) Hypertension – ACE inhibitors or angiotensin II receptor antagonists. (iii) Acute renal failure – See renal failure.
6. *Dialysis* – if unconscious, twitching or deteriorating patient, rapidly rising blood urea or rising serum potassium. In children peritoneal dialysis is preferred to haemodialysis.
7. *Transplantation* for those who progress to ESKF. Some forms of GN tend to occur in transplanted kidneys.

Subtypes of GN – Using histological analysis, it is possible to identify subtypes of GN with particular pattern of glomerular injury. Although there is some overlap in presentation treatment and prognosis, these subtypes have certain distinguishing features.

Following are types of glomerulonephritis which presents with acute nephritc syndrome:

IgA nephropathy – is the most common type of GN. It presents with hematuria, which may be macroscopic, particularly after recurrent infections. Prognosis is generally good if no associated proteinuria, hypertension or impairment of excretory renal function. If proteinuria is more than 1 g/24 hours, risk of eventual ESRF is about 25%.

Renal biopsy – Deposition of polymeric IgA in the glomerulus, usually associated with proliferation of intrinsic glomerular cells is pathognomonic. Aetiology is unknown, but there is evidence that primary abnormality is in the IgA system rather than in the kidney. An identical glomerular lesion is seen in Henoch-Schonlein purpura.

Management – There is no proven treatment. Fish oils may protect renal function in poor prognosis subgroups. ACE inhibitors are antihypertensive agents of choice. In

case of rapidly progressive glomerulonephritis, steroid and plasmapheresis should be considered.

Mesangiocapillary GN (MCGN, membranoproliferative GN) – is uncommon. There are three subtypes, with indistinguishable clinical presentations (proteinuria, hematuria, hypertension, impaired renal function) and findings on histology. The subtypes are defined according to appearances on electron microscopy, and probably have different pathogenesis. MCGN is associated with activation of the complement cascade – the classical pathway in type I MCGN, alternative pathway in type II and terminal pathway in type III. Types II and III MPGN are usually idiopathic, except in patients with complement factor H deficiency, in the presence of C3 nephritic factor and/or in partial lipodystrophy producing type II disease or complement receptor deficiency in type III disease.

Type II MCGN may be associated with partial lipodystrophy in which selective loss of fat cells in the face and upper trunk occur giving patients a characteristic cadaveric appearance. Secondary forms of MCGN are usually of type I pattern and result from chronic infections (e.g. infective endocarditis, visceral abscesses, infected prosthetic materials) or cyroglobulinaemia (which may complicate infections particularly hepatitis C).

On renal biopsy: 1. Type I MPGN, there is mesangial proliferation with lobular segmentation and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes, called "tram-tracking". 2. Type II MPGN, biopsy shows a dense thickening of the GBM containing ribbons of dense deposits and C3, sometimes called "dense deposit disease." 3. In Type III MPGN, proliferation is less common than the other two types and is often focal; mesangial interposition is rare and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

All types of MCGN tend to have a progressive course; up to 50% develop chronic renal failure within 10 years.

Management – Control BP with ACE inhibitors and treat other complications (e.g. hypercholesterolaemia). High-dose corticosteroids are not always effective. Therapy aimed at blocking complement activity may be useful. In secondary MPGN, treating underlying condition is important.

Focal necrotizing GN – FNGN is the renal lesion associated with the clinical syndrome of rapidly progressive GN (RPGN) and is a medical emergency. Severe acute inflammation occurs in the glomerulus, sometimes with formation of 'crescents' when the glomerulus is squashed by cells that fill Bowman's space; these cells are a mixture of infiltrating inflammatory cells and proliferating resident cells. ARF can occur without crescents if glomerular necrosis is sufficiently severe.

If antibodies to glomerular basement membrane (GBM) are present, the glomerulus shows linear deposition of IgG. More commonly there is no immunoglobulin in the glomerulus and the condition is termed (pauci-immune FNGN); these patients typically exhibit circulating antineutrophil cytoplasmic antibodies (ANCA).

Anti-GBM disease is the only form of GN in which the pathogenesis is fully understood and treatment rational (plasma exchange to remove circulating antibody, corticosteroids to suppress inflammation, cyclophosphamide to suppress further antibody synthesis).

Small vessel vasculitis – Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis are small vessel vasculitides usually associated with ANCA. The renal manifestations in all three diseases are hematuria and proteinuria, often with rapid deterioration of excretory renal function. Focal segmental necrosis of glomerular capillaries with crescent formation but without immune deposits (segmental necrotizing glomerulonephritis), is characteristic on kidney histology. On biopsy, Wegener's granulomatosis is differentiated from other small vessel vasculitis by presence of noncaseating granuloma. Diagnosis is confirmed by detection of ANCA by indirect immunofluorescence or enzyme-linked immunosorbent assay.

Management – Initial therapy (remission induction) requires high-dose cyclophosphamide and corticosteroids. Plasma exchange results in significant improvement. In those with less advanced renal involvement (creatinine < 5.6 mg/100 ml). Prednisolone 1 mg/kg/day PO to maximum of 80 mg/day; dose reduced to 12.5-15 mg/day by 3 months plus Cyclophosphamide 2.5 mg/day. During cyclophosphamide therapy, cotrimoxazole 480 mg 3 times per week for prophylaxis of *Pneumocystis jiroveci,* Nocardia and nasal streptococcus aureus infections. WBC count is monitored weekly. Cyclophosphamide should be continued for up to 3 months. If clinical remission is achieved, cyclophosphamide is replaced with azathioprine 2–3 mg/day initially, reduced to 1.5 mg/kg/day by the end of the first year. Later, if patient is both clinically in remission and ANCA negative, both azathioprine and prednisolone are slowly reduced and then stopped.

In patients intolerant to azathioprine, mycophenolate mofetil may be tried starting at 250 mg PO b.d. and increasing to 1 g b.d. over 3–4 weeks.

Post-infectious GN – Proliferative GN is seen in association with certain infections particularly streptococcal throat infections, also staphylococcus, influenza B, certain parasites. Usual presentation is with *acute nephritic syndrome.* (Refer to Acute GN).

Causes

1. *Primary renal disease* – Idiopathic, immune complex, anti-GBM nephritis.
2. *Secondary extrarenal disease* – (a) Infections – PSGN, infective endocarditis, shunt nephritis, visceral sepsis, hepatitis. (b) Multisystem disease – SLE, Henoch-Schonlein purpura, Wegener's granulomatosis, polyarteritis nodosa, disseminated intravascular coagulation, accelerated hypertension.

Clinical features

Hypertension, oedema, proteinuria and microscopic haematuria continue till the patient dies of renal failure or hypertension in 6–18 months after initial attack. Death from uraemia occurs in about 1½–2 years of onset.

Renal biopsy — Demonstrates hypercellularity of mesangial and endothelial cells, glomerular infiltrates of polymorphonuclear leukocytes, granular subendothelial immune deposits of IgG, IgM, C3, C4 and C5-9 and subepithelial deposits (which appear as "humps"). In endocarditis related glomerulonephritis, foci of necrosis is seen.

Treatment

Plasma exchange (2–4 litres of plasmapheresis daily) combined with corticosteroids and cyclophosphamide in patients with diffuse crescentic glomerulonephritis. Also anticoagulants, like heparin and warfarin and antithrombotic agent such as clopidogrel because of involvement of coagulation process in crescent formation. Table 8 lists renal diseases requiring plasmapheresis.

Table 8: Indications of plasmapheresis in renal disease

Anti-GBM nephritis.
Rapidly progressive GN.
Goodpasture's syndrome.
Polyarteritis nodosa and other vasculitides
Systemic lupus erythematosus.
Thrombotic thrombocytopenic purpura.
Haemolytic-uraemic syndrome.
Scleroderma.
Acute renal allograft rejection.

Nephrotic Syndrome (NS)

A clinical condition in which there is oedema, proteinuria and hypoproteinaemia and hyperlipidaemia irrespective of aetiology or any other additional abnormal clinical features. Over 80% of patients with nephrotic syndrome have idiopathic glomerular lesions.

Causes

1. ***Primary glomerular diseases***
   - Minimal change nephropathy.
   - Mesangioproliferative glomerulonephritis.
   - Membranous nephropathy.
   - Focal and segmental glomerulosclerosis.
   - Crescentic glomerulonephritis.
2. ***Idiopathic***
3. ***Secondary to other diseases***
   - *Infections* – Malaria, hepatitis B, herpes zoster, streptococcal and staphylococcal infections, syphilis, leprosy, schistosomiasis.
   - *Drugs* – NSAIDs. Heavy metals such as gold, anticonvulsants (especially phenytoin and troxidone), penicillamine, ACE inhibitors, heroin, rifampicin, tolbutamide and probenecid.
   - *Malignancy* – Hodgkin's disease and other lymphomas.
   - *Systemic diseases* – Diabetes mellitus, amyloidosis, SLE, Henoch-Schonlein purpura, cyroglobulinaemia, polyarteritis nodosa.
   - *Familial disorders* – Congenital (neonatal) nephrotic syndrome, Airport's syndrome, Fabry's disease.
   - *Miscellaneous conditions* – Reflux nephropathy, renal vein thrombosis, toxaemia of pregnancy, allergic reactions to insect bites, pollens and vaccines, renal artery stenosis.

Minimal change nephropathy (MCN)

It is a most common cause of nephrotic syndrome in children. It can be primary or secondary to other diseases like Hodgkin's lymphoma. On renal biopsy, under light microscopy it doesn't show abnormal lesion; hence it is also called "Nil lesion". Under electron microscope effacement foot processes of podocytes is seen.

Treatment

Steroids (Prednisone) is mainstay of treatment. Among these patients few become steroid dependent and relapse on steroid tapering. In case of non responders or steroid resistance diagnosis of FSGS is considered and repeat biopsy done to confirm diagnosis.

Focal segmental glomerulosclerosis (FSGS) – typically presents with nephrotic syndrome, and is more likely than minimal change nephropathy to be associated with hypertension, microscopic hematuria, impaired excretory renal function and/or corticosteroid resistance. It tends to recur after renal transplantation; there is evidence for a circulating permeability factor in these cases, removal of which by plasmapheresis leads to temporary reduction in proteinuria.

Histology – Areas of scarring in glomeruli; the sclerotic changes are focal (affecting some glomeruli) and segmental (affecting only parts of each glomerulus). Similar glomerular changes are seen as a secondary phenomenon when the number of functioning nephrons is reduced (e.g. as a result of nephrectomy, ischaemia or another primary renal disease), leading to the hypothesis that FSGS results from 'overloading' of the remaining nephrons. Similar changes may be seen in association with extreme obesity. A variant of FSGS has been recognized in association with HIV infection – the so-called 'collapsing' FSGS, the glomerulus collapses as a result of proliferation of surrounding epithelial cells, filling Bowman's space. Other variants are endocapillary hypercellularity and glomerular tip lesion.

Management – In primary FSGS, prolonged courses of high dose corticosteroids is used to induce remission of nephrotic syndrome. Cyclosporine 3-5 mg/kg/day for 4–12 months, may induce remission. An ACE inhibitor to reduce proteinuria and statins for hyperlipidaemia should also be given. Disease often progresses; ESRF develops within 10 years in about 50% of patients.

In secondary FSGS, management is treating underlying cause and there is no role of steroids and immunosuppressant.

Membranous nephropathy (MN) – typically presents with proteinuria, which may be asymptomatic or severe enough to cause nephrotic syndrome. Microscopic hematuria, hypertension and/or impaired excretory renal function may be associated. Identical glomerular histology is seen in the primary (idiopathic) form, and when MN is secondary to drugs (particularly NSAIDs, gold, penicillamine), solid organ tumours particularly carcinoma of bronchus or breast, infection (particularly hepatitis B) or hypothyroidism and rheumatological diseases like lupus. Susceptibility to idiopathic MN and to some forms of secondary MN is closely linked to the MHC allele DR3, strongly suggesting that shared immunological mechanisms are operating.

On renal biopsy, it shows uniform thickening of the basement membrane along the peripheral capillary loops under light microscopy; this thickening needs to be distinguished from that seen in diabetes and amyloidosis. Immunofluorescence demonstrates diffuse granular deposits of IgG and C3 and electron microscopy typically reveals electron-dense subepithelial deposits. Degree of tubular atrophy and interstitial fibrosis are predictive of progression of disease.

Management – If MN is secondary to drugs, complete resolution is expected when the same is withdrawn. Treatment is reserved for those with poor prognostic signs (deteriorating excretory renal function and/or severe nephrotic syndrome). Combination of prednisolone and chlorambucil in alternating monthly cycles for a total of 6 months. Cyclophosphamide, mycophenolate mofetil and cyclosporine can be used. In cases, that relapse or fail to respond Rituximab (anti-CD20 antibody) can be used. ACE inhibitors reduce proteinuria and may slow progress of renal insufficiency. Nephrotic syndrome caused by membranous GN is associated with risk of thrombotic complications and anticoagulants may be prescribed.

Pathology – The kidneys are large, pale and soft. Biopsy studies show a wide variety of histopathological changes – (a) Minimal change nephropathy is common in very young children. (b) Focal glomerulosclerosis. (c) Membranous nephropathy. (d) Proliferative glomerulosclerosis – accounts probably for the largest group of adults with idiopathic nephrotic syndrome.

Clinical Features

1. *Age and sex* – Two to three times more common in childhood with peak incidence at 2–3 years. In this age group, there is a male: female ratio of 2.5: 1, in adults, sex incidence is equal.
2. *Oedema* – is peripheral involving the limbs, particularly lower limbs. In children, oedema may be more obvious in the face and abdomen. Usuallymassive generalized anasarca, the patient almost weighing double his true weight. Intense oedema of the scrotum or vulva may occur. There may be bilateral hydrothorax. Oedema may persist for many weeks or months. Spontaneous subsidence with diuresis (nephrotic crisis) may occur, to befollowed again by increase of oedema.
3. *GI symptoms* – Anorexia causes severe malnutrition. Diarrhoea and vomiting due to oedema of intestinal wall.
4. *General symptoms* – Prolonged protein loss causes anorexia, lethargy, tiredness, frequent infections and muscle wasting. Dyspnoea may occur if there is fluid in the pleural cavity.

5. *Blood pressure* – There may be periods of hypertension; ultimately with development of chronic nephritis permanent hypertension may develop.

Laboratory Findings

1. *Urine* – (i) Oliguria while oedema is forming, diuresis or normal amount of urine during period of subsidence of oedema. (ii) Proteinuria – Massive, usually more than 5 g/day though variable from time to time; urine becomes almost solid on boiling. Daily loss of protein may be 20–50 g. (iii) Red blood cells absent or few. (iv) Casts – Fatty casts, tubular cells, oval fat bodies, doubly refractile bodies.
2. *Blood* – (i) Anaemia – Slight, normochromic. (ii) Hypoalbuminaemia – Serum albumin usually less than 3 g/100 mL. Total serum globulin concentration frequently lowered with often elevation of α2 and β globulins. (iii) Hyperlipoproteinaemia (LDL level in particular) and hyperfibrinogenaemia (contributing to raised ESR).
3. *Renal biopsy* – is normal on light microscopy but electron microscopy shows typical abnormalities (effacement of epithelial cell foot processes).

Differential Diagnosis

1. *From acute nephritic syndrome* Table 9 lists the differences between acute nephritic syndrome and nephrotic syndrome
2. *Of conditions causing nephrotic syndrome* – Cases due to diabetes, anaphylactoid purpura, drug therapy or irradiation of the kidneys can be diagnosed from the history or other typical findings. Amyloid disease – history of chronic suppuration; positive liver or gum biopsy or renal biopsy. In thrombosis of renal vein, there is evidence of inferior vena caval thrombosis or presence of only one kidney. Polyarteritis can be diagnosed from other characteristic features like fever, peripheral neuritis etc., or positive muscle biopsy. Disseminated lupus – Anti-dsDNA and anti-SM antibodies.
3. *Of generalized anasarca.*

Complications

1. *Protein malnutrition* – Wasting, striae, osteoporosis, poor wound healing.
2. *Hypercoagulability* – Spontaneous venous and arterial thrombosis due to rise of many clotting factors in plasma including fibrinogen and factor VIII.
3. *Impaired resistance to infection* – Cellulitis, primary peritonitis with pneumococci, urinary tract infection.

Table 9: Differences between acute nephritic syndrome and nephrotic syndrome

	Acute nephritic syndrome	*Nephrotic syndrome*
Previous illness	Preceding streptococcal infection	No previous illness
Age	Predominantly school-going child	Most often seen in pre-school child
Onset	Sudden	Insidious
Oedema	Rarely severe	Presenting feature and rapidly becomes massive
Hypertension	Invariably present	Usually absent
Urine	Many red cells	Few red cells
Azotaemia	Present	Absent
Recovery	In 90%	May occur
Death	Due to uraemia or left ventricular failure.	Uraemia may develop after months or years. Secondary infections common.

4. *Acute hypovolaemia* – may occasionally be severe enough to precipitate renal failure.
5. *Hyperlipidaemia* – probably increased atherogenesis.

Prognosis – With minimal lesion nephrotic syndrome, about 90% of children respond to prednisolone. In adults the response rate is about 60%. Relapse rate is high, particularly in children and constant steroid administration may be necessary to prevent relapses. The long-term prognosis for renal function is excellent. Progression to renal failure does not occur unless the morphology alters and progressive lesions of focal and segmental hyalinosis and sclerosis develop. This is uncommon in those who show an initial response to corticosteroids, it is much more likely among non-responders. Prolonged heavy proteinuria may be one of the factors responsible for the progressive glomerular lesion.

Management

Corticosteroids – produce rapid and complete remission with clearing of proteinuria in 90% cases. Dose – Prednisolone 1 mg/kg/day, maximum 80 mg/day. Remission usually occurs between days 7 and 14, though some patients need up to 16 weeks therapy to achieve complete remission. After disappearance of proteinuria, or one week after remission, prednisolone dose is reduced to 0.5 mg/kg/day and then tapered slowly. An attempt to stop

treatment should be made after 8 weeks. In patients who relapse, course of prednisolone should be repeated.

Immunosuppressive drugs – In steroid-resistant patients, or in those in whom remission can only be maintained by heavy doses of steroids, cyclophosphamide 1.5–2 mg/kg/day for 8-12 weeks with concomitant prednisolone 7.5–15 mg/day. The neutrophil count must be checked every 2 weeks and cyclophosphamide stopped if it falls below $2 \times 10^3/mm^3$.

Cyclosporine 3–5 mg/kg/day is effective in some corticosteroid resistant or dependent patients.

Prednisolone 7.5–15 mg/day is also given.

Levamisole – In corticosteroid dependent children 2.5 mg/kg to maximum 150 mg on alternate days is useful in maintenance of remission.

4. ACUTE RENAL FAILURE (ARF)

ARF may be defined as any sudden fall in GFR sufficient to cause uraemia. Oliguria (< 15 mL/hour) is a feature in many patients. 'Non-oliguric' renal failure is seen, particularly in patients with severe burns, nephrotoxic damage (particularly due to aminoglycosides, and radiographic contrast media), oliguric renal failure that may be converted to non-oliguric failure by aggressive management with fluids, diuretics and other agents.

PATHOPHYSIOLOGY

Pre-renal ARF is an appropriate physiological response to effective or true hypovolaemia, resulting in intense renal conservation of sodium and water at the expense of decreased GRF. Urea clearance decreases more than creatinine clearance as a result of action of ADH. Renal function returns rapidly to normal once the underlying cause is corrected. Reduction in renal arterial perfusion pressure below the level at which autoregulation of GRF occurs is an important contributor. However, in hypovolaemic or septic patients, pre-renal ARF may still occur as a result of intra-renal vasoconstriction.

Acute tubular necrosis (ATN) results from the insults that cause pre-renal ARF, but lasting long enough to cause ischaemic injury to renal tubules. This results in long-lasting reduction in GFR. This is caused by a combination of:

- Persistent, intense intra-renal vasoconstriction caused by endothelin, other autocrine mediators and increased intracellular calcium.
- Loss of polarity of tubular cells, leading to loss of function
- Loss of adherence of tubular cells, leading to desquamation into the tubular lumen
- Formation of tubular casts, blocking the lumen and preventing urine flow
- Tubuloglomerular feedback (reflex reduction of glomerular filtration due to high sodium concentration in distal tubule)
- Back-leak of tubular filtrate as a result of loss of tubular viability and obstructing casts
- Reperfusion injury, causing oxidant stress

Intrinsic renal disease. The diseases listed as causes, cause ARF by numerous mechanisms, including:

- Destruction of glomeruli
- Renal arterial vasoconstriction (e.g. contrast nephropathy)
- Ischaemic damage resulting in ATN
- Direct tubular toxicity, resulting in an ATN-like syndrome

Post-renal ARF. Increased pressure within the renal collecting systems results in reduced GRF, reduced tubular reabsorption of sodium and water, and acquired renal tubular acidosis, phosphaturia and other abnormalities of tubular function. In addition, obstruction leads to tubulointerstitial inflammation, caused by infiltrating macrophages and T lymphocytes and followed by fibrosis, resulting in incomplete recovery of renal function if obstruction is not rapidly relieved.

AETIOLOGY

Causes of acute renal failure are listed in Table 10.

Causes of acute renal failure in tropical and developing countries

- Diarrhoeal illness
- Shigella dysenteriae type 1, Salmonella typhi and other infections. Haemolytic-uraemic syndrome
- *G-6-PD deficiency and drugs*: Massive intravascular haemolysis and haemoglobinuria
- Snake bite: Direct nephrotoxicity, myoglobinuria, haemolysis, DIC
- Plasmodium falciparum malaria: Intravascular haemolysis, intravascular sequestration of parasitized RBCs
- Herbal remedies (e.g. djenkol bean, marking nut tree): Acute tubular necrosis
- Paraquat and copper sulphate poisoning
- Melioidosis: Haemolysis, direct nephrotoxicity

Table 10: Causes of acute renal failure

Hypovolaemia
• Haemorrhage
• Volume depletion (vomiting, diarrhoea, inappropriate diuresis, burns)
Renal hypoperfusion
• NSAIDs, cyclooxygenase 2 inhibitors
• Angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists
• Abdominal aortic aneurysm
• Renal artery stenosis/occlusion
• Hepatorenal syndrome
Hypotension
• Cardiogenic shock
• Distributive shock (Sepsis, anaphylaxis)
Oedematous states
• Cardiac failure
• Hepatic cirrhosis
• Nephrotic syndrome
'Intrinsic' renal failure
Glomerular disease
• Inflammatory – Post-infectious GN, cryoglobulinaemia, Henoch-Schonlein purpura, SLE, antineutrophil cytoplasmic antibody associated GN, anti-glomerular basement membrane disease
• Thrombosis – DIC, thrombotic microangiopathy
Interstitial nephritis
• Drug-induced – NSAIDs, antibiotics
• Infiltrative – Lymphoma
• Granulomatous – Sarcoidosis, tuberculosis
• Infection related – Post-infective, pyelonephritis
Tubular injury
• Ischaemia – Prolonged renal hypoperfusion
• Toxins – Drugs e.g. aminoglycosides, radiocontrast media, pigments (such as myoglobin), heavy metal (e.g. cisplatin)
• Metabolic – Hypercalcaemia, immunoglobulin light chains
• Crystals – Urate, oxalate
Vascular
• Vasculitis (usually associated with antineutrophil cytoplasmic antibody)
• Cyroglobulinaemia
• Polyarteritis nodosa
• Thrombotic microangiopathy
• Cholesterol emboli
• Renal artery or renal vein thrombosis
• Malignant hypertension
Post-renal
Intrinsic
• Intra-luminal – Stone, blood clot, papillary necrosis
• Intra-mural – Urethral stricture, prostatic hypertrophy or malignancy, bladder tumour, radiation fibrosis
Extrinsic
• Pelvic malignancy
• Retroperitoneal fibrosis

- Leptospira interrogans: Acute interstitial nephritis, acute tubular necrosis
- lschistosoma haematobium: Ureteral stenosis with obstructive nephropathy
- Heat stroke: Rhabdomyolysis and DIC

Pre-renal ARF is defined as a reduction in GFR caused by impaired renal perfusion as a result of hypotension or hypovolaemia or renal artery stenosis that is rapidly reversed by correction of underlying cause.

CLINICAL FEATURES – STAGES

Early or pre-oliguric stage

This is overshadowed by symptoms of the primary cause. Symptoms like lethargy, nausea, headache, are indicative of overhydration and should arouse suspicion of impending renal insufficiency. Restoration of renal perfusion leads to rapid recovery of renal function.

Oliguric stage

a. *Oliguria* – (less than 400 mL urine in 24 hours in adults) sets in majority within 24–48 hours. The duration varies, average being 4–10 days. Complete anuria is rare and indicates either a severe renal catastrophe or obstructive aetiology.
b. *Gastrointestinal* – Anorexia, nausea, vomiting; at times diarrhoea, mouth ulceration, dynamic ileus or pseudo-peritonitis if these are related to uncontrolled uraemia, they disappear after dialysis.
c. *Circulatory* – Hypertension is common in acute glomerulonephritis, renal infarct and cortical necrosis and when ARF results from intoxication by organic solvents. Severe hypertension is usual in malignant nephrosclerosis or thrombotic microangiopathy. Pericarditis is uncommon.
d. *Respiratory* – Dyspnoea is related to metabolic acidosis, to pulmonary infection or oedema.
e. *Neuromuscular* – Drowsiness, confusion and agitation occur in advanced uraemia and may indicate water or drug intoxication. Convulsions, coma or focal neurological signs may also be observed. Muscular twitching or cramps are uncommon in absence of plasma electrolyte disorders.
f. *Infection* – Secondary sepsis is a major risk in patients with ARF.

Diuretic stage

This phase of the disease is ushered in by increase in urinary output to about 1000 mL in 24 hours; this

may progress to polyuria. Febrile reaction is common and uraemic symptoms may be aggravated and lead to coma. With profound diuresis dehydration may set in.

DISTINGUISHING ARF FROM CKD

Renal Ultrasonography

- Reduced renal volume, length or cortical thickness, together with increased echogenicity, is a feature of many types of CRF, through renal size may remain normal is CRF (e.g. diabetic nephropathy, amyloidosis).
- Renal swelling is only seen in ARF.
- Renal size is normal in most patients with ARF.

Anaemia is a feature of CRF

Bone disease. Radiological evidence of hyperparathyroidism, very high PTH levels is diagnostic of CRF, but hypocalcaemia and hyperphosphataemia may occur in both ARF and CRF.

Investigations

Table 11 enumerates the investigation that can be done in acute renal failure.

MANAGEMENT

Early Management

1. ***Restoration of fluid and electrolyte balance*** –There are two good physical signs of volume depletion – (a) Low jugular venous pressure. (b) Postural drop in BP. Blood pressure, forexample, 120–80 may be regarded as unremarkable in recumbent position; significant volume depletion may be recognized only when BP. falls substantially as the patient sits or stands.

   Intravascular volume depletion should be corrected rapidly. If large veins in forearms or antecubital fossa are not available, access should be established through femoral vein.

Table 11: Investigation in acute renal failure

Test	*Comment*
Urinalysis	
Dipstick for blood, protein, or both Microscopy for cells, casts, crystals	Suggests a renal inflammatory process Red cell casts diagnostic in glomerulonephritis
Biochemistry	
Serial urea, creatinine, electrolytes metabolic Blood gas analysis, serum bicarbonate Creatine kinase, myoglobinuria rhabdomyolysis C-reactive protein Serum immunoglobulins, serum protein and electrophoresis, Bence-Jones proteinuria	Important metabolic consequences of ARF include hyperkalaemia, Acidosis, hypocalcaemia, hyperphosphataemia Markedly elevated creatine kinase and myoglobinuria suggests Non-specific marker of infection or inflammation Immune paresis, monoclonal band on serum protein electrophoresis, Bence-Jones proteinuria suggests myeloma
Haematology	
Full blood count, blood film embolisation, microangiopathy Coagulation studies	Eosinophilia may be present in acute interstitial nephritis, cholesterol or vasculitis Thrombocytopenia red cell fragments suggest thrombotic Disseminated intravascular coagulation associated with sepsis
Immunology	
Antinuclear antibody (ANA) Anti-double stranded (ds) DNA antibodies Antineutrophil cytoplasmic antibody (ANCA), Antiproteinase 3 (PR3) antibodies, Antimyeloperoxidase (MPO) antibodies Complement concentrations Antiglomerular basement membrane antibodies Antistreptolysin O and anti-DNAse B titres Virology Hepatitis B and C; HIV Radiology	ANA positive in SLE and other autoimmune disorders; anti-dsDNA antibodies more specific of SLE Associated with systemic vasculitis; c-ANCA and anti-PR3 antibodies associated with Wegener's granulomatosis; p-ANACA and anti-MPO antibodies present in microscopic polyangiitis Low in SLE, acute postinfectious glomerulonephritis, cryoglobulinaemia Present in Goodpasture's disease High after streptococcal infection Important implications for infection control within dialysis area Renal size, symmetry, evidence of obstruction
Kidney biopsy antibodies,	If clinical suspicion of PRGN (e.g. positive antineutrophil cytoplasm hematuria and proteinuria, raised C-reactive protein)
Differentiating features between pre-renal and renal causes of ARF in an oliguric patient are given in Table 12.	

Table 12: Differentiating features between pre-renal and renal causes of ARF in an oliguric patient

	Pre-renal	*Renal*
Identifiable causes (shock, hypovolaemia)	*Yes*	*No*
Urine		
Protein	0-1	1–4
RBCs	0	1–3
WBCs	0	1–3
Casts	0–1	1–3
Osmolality	> 500	< 400
Sodium	< 20	> 35
Urine/urea ratio	> 18	< 3
Urea/creatinine ratio	> 40	< 20
Fractional excretion of sodium	< 1%	> 1%

2. ***Other measures*** – If oliguria persists after adequate circulation is established in order to increase renal tubular flow and promote glomerular vasodilatation. Fluids restricted to previous 24-hr urine volume plus other losses. Sodium and potassium restricted to <80 mmol/day and 60 mmol/day respectively:
   a. *Mannitol* – 100–150 mL of 10% solution or 50 mL of 20% solution (maximal dose 50 g/24 hours), after shock and/or fluid depletion has been treated and urinary obstruction excluded. If urine flow exceeds 50 mL/hour, further doses should be given 3 or 4 hours later to maintain an output of about 100 mL/hour. Mannitol can also be used to determine whether renal failure is due to dehydration. Infusion of 100 mL 20% mannitol over 15 minutes should result in a diuresis of 100 mL in the next 2 hours in the presence of dehydration but not if there is renal impairment.
   b. *Frusemide* – in large doses is equally effective. Shock, hypotension or fluid depletion must be excluded or corrected first. A first dose of 100–200 mg IV (or 250–500 mg by mouth) is followed every 3–4 hours by equal doses if urine flow increases. Urinary losses of water, electrolytes must be replaced by 5% dextrose containing 4–6 g. litre NaCl and 1–1.6 g/litre KCl, adjusted to the actual urinary output.
   c. *Dopamine* – 2.5 µg/kg/minute, if oliguria persists after adequate circulation has been established.

Management of Established ARF

1. ***Recognition and treatment of life-threatening complications***

   Hyperkalaemia – can cause cardiac arrest, the risk of which can be judged by ECG manifestations (no P waves, widened QRS complexes and tenting of T waves) requires immediate treatment:
   - IV calcium (10% calcium gluconate, 10 mL over }1 minute given immediately and repeated until ECG improves), this acts instantly to 'stabilize' the cardiac membranes, but does not alter serum potassium level.
   - IV insulin and glucose (rapidly acting insulin 10 U, with 50% glucose, 50 mL over 5-10 minutes, after IV calcium). This reduces serum concentration by 1–2 mmol/1 over 1/2–1 hour.
   - If rapid recovery does not occur, hyperkalaemia will recur and further treatment is required:
   - Haemodialysis/haemofiltration
   - Cation exchange resins (sodium or calcium polystyrene sulphonate 15 g PO q6h or 15–30 g p.r. 6-hourly). These require 4 hours for effect and lead to severe constipation if taken without laxatives (e.g. lactulose 10–15 mL)

   Pulmonary oedema – is the most serious complication of salt and water overload when IV fluids are administered to patients with oliguric renal failure.
2. ***Fluid and electrolytes*** – After initial resuscitation, fluid and electrolyte input depends on output. A satisfactory regimen is to give in 24 hours a volume equal to total fluid output from the kidneys and GI tract in previous 24 hours with additional 500–1000 mL for insensible loss. Alternate administration of 0.9% saline and 5% dextrose provide sufficient sodium in most patients. Potassium supplement is seldom required and must be monitored.
3. ***Nutrition*** – Adequate caloric intake to minimise endogenous protein catabolism and acidosis. (i) If ARF not severe – 30 kcal/kg/day and 0.5 g/kg/day of protein (2,000 kcal and 30 g protein/day for an adult). If anorexia is pronounced feeding can be done through a gastric tube. (ii) If ARF is severe – (e.g. post-traumatic or surgical), 50 kcal/kg/day and 1 g/kg/day of protein may be required to obtain a positive nitrogen balance. Since fluid must be restricted, parenteral fluid using dextrose-rich solutions and amino-acid mixtures is often indicated.

   According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, patients with AKI should achieve a total energy intake of 20–30 kcal/kg per day. Protein intake should vary depending on the severity of AKI: 0.8–1.0 g/kg per day in noncatabolic AKI without the need for dialysis; 1.0–1.5 g/kg per day in patients on dialysis and up to a maximum of 1.7 g/kg per day if hypercatabolic and receiving continuous renal replacement therapy.

4. ***Antibiotics*** – because infection is a major complication. Aminoglycosides, tetracyclines (except doxycycline), cephaloridine and cephalexin, and amphotericin B must be avoided. Unexplained fever, particularly if accompanied by toxic manifestations, is highly suggestive of undetected abscess which requires drainage.
5. ***Other measures*** – (i) For nausea and vomiting – Domperidone 10 mg IM. (ii) For sedation and fits – Diazepam. (iii) Anaemia – Packed red blood cells. (iv) H_2-receptor antagonists or sucralfate – for preventing bleeding from stress ulcers especially in post-trauma and surgical patients.
6. ***Monitoring*** – Daily monitoring of body weight, fluid balance, urea, electrolytes, creatinine. Full blood count and culture of all secretions and wounds, and twice weekly calcium, phosphate and LFTs.
7. ***Watch for complications*** – of the causative condition (particularly persisting sepsis, fungal superinfection, muscle compartment syndromes) and for complications of treatment (line sepsis, antibiotic colitis, metabolic complications of parenteral nutrition). Hypercatabolism is an important clue to occult infection if other causes (GI bleeding, inadequate nutrition, injured or necrotic tissue, drugs such as corticosteroids and tetracycline) have been excluded. Febrile patients require chest radiographs, measurement of C-reactive protein (>100 mg/L is suggestive of septicaemia) and cultures of sputum, urine, blood and operative wound sites. Abdominal ultrasound and CT scan may be required to detect intra-abdominal infection.
8. ***Renal replacement therapy (RRT)*** – is urgently required if there is hyperkalaemia, rapidly increasing serum creatinine, oliguria (particularly in those with impending or established pulmonary oedema) and severe metabolic acidosis.

   Options are usually continuous haemofiltration (more commonly used in ICUs) and intermittent haemodialysis. Peritoneal dialysis is often complicated by fluid leaks, difficulty in achieving satisfactory fluid balance, and infection. Haemodialysis using biocompatible membranes and highly purified water for dialysate preparation gives better outcomes than conventional dialysis.

Management of Diuretic Phase

Fluid and electrolyte replacement during this stage must be based more on clinical observation such as general condition, pulse, blood pressure and thirst, and biochemical observations rather than on quantitative and qualitative loss of water and electrolytes in urine. Intravenous therapy is stopped and the patient encouraged to take a high potassium, high salt diet and liberal intake of water (about 3000 mL). Infection remains a problem during this phase. Dialysis should be continued until there is a spontaneous drop in creatinine and urea. Early ambulation and return to normal dietary habits should be allowed as soon as possible.

5. CHRONIC KIDNEY DISEASE (CKD)

CKD: Stages (NKF/K/DOQI) Classification:

Stage *GFR*

1. > 90 mL/min → Kidney damage with N or ↑ GFR
2. 60–89 mL/min → Kidney damage with mild ↓ GFR
3. 30–59 mL/min – Moderate ↓ GFR
4. 15–29 mL/min – Severe ↓ GFR
5. 15 mL/min – Dialysis required

CAUSES

Common

- Glomerulonephritis
- Diabetic nephropathy
- Hypertensive renal disease

Uncommon

- Renovascular disease (especially in elderly)
- Acute interstitial nephritis and other drug reactions
- Vasculitis in the kidney (e.g. Wegener's granulomatosis, microscopic polyangiitis)
- Obstructive uropathy

  Congenital lesions and reflux nephropathy in children

  Prostatic obstruction in elderly

Pathogenesis – of clinical syndrome of CKD:

1. *Uraemic toxins* – Fall in glomerular filtration rate and reduction in renal tubular secretory capacity prevent certain substances from being excreted by the kidney and these probably produce their adverse effects on every organ of the body. However, studies of the effects of dialysis, dietary modifications and transplantation have not identified the toxins involved.
2. *Electrolyte and water excretion* – Limited ability of diseased kidney to manipulate electrolyte and water excretion appropriately may lead to either salt and water retention with oedema and circulatory congestion, or to salt depletion.
3. *Erythropoietin and 25-hydroxy-cholecalciferol* – There is impaired production of erythropoietin and reduced hydroxylation of 25-hydroxy-cholecalciferol to 1,25 dihydroxycholecalciferol, the most active metabolite of vitamin D, a step which normally occurs in the kidney.

4. *Renin* – Impaired perfusion of remaining renal tissue may stimulate the inappropriate release of renin.
5. *PTH* – One of the principal disturbances of endocrine function in CKF is marked hyperplasia of parathyroid glands with very high levels of PTH. This contributes to renal osteodystrophy, soft tissue calcification and bone necrosis in CKF and also probably to pruritus, anaemia, hyperlipidaemia, neurological disturbances and sexual dysfunction. However, patients with primary hyperparathyroidism manifest few of these disturbances and the role of PTH in uraemic toxicity is still uncertain.
6. *'Middle molecules'* – The middle molecule hypothesis is based on the apparent absence of neuropathy in patients on chronic peritoneal dialysis (which is less efficient than haemodialysis in removing small molecules, but more efficient for middle molecules), and the high risk of neuropathy in patients treated with small surface area dialysers. Also the observation that when weekly haemodialysis time was markedly reduced, neuropathy did not appear, provided a membrane highly permeable to middle molecules was used. While the identity of uraemic toxins is largely unknown, it is suggested that some dialysis schedules permit accumulation in body fluids of molecules in the range 1,000 to 2,000 daltons, and these cause some of the uraemic problems encountered by patients on regular dialysis.

STAGES

Chronic progressive renal disease has four stages:

1. *Diminished renal reserve* – About 50–70% of kidney function has to be lost before the effect on blood chemistry becomes readily detectable, e.g. by rise of blood urea.
2. *Renal insufficiency* – from loss of further kidney function. There is moderate nitrogen retention (blood urea 50–100 mg/100 mL, plasma creatinine 1.5–2.5 mg/100 mL) and mild acidosis may occur. Usually no symptoms except nocturia. Hypertension may dominate the clinical picture.
3. *CKF* – As renal function declines, a broader range of biochemical abnormalities develop. However symptoms may be absent or slight. Patients often have hyperphosphataemia and hypocalcaemia, because GFR, renal tubular responses and hormonal action are not capable of maintaining homeostasis. Anaemia is common, but because the main underlying process involves decreased production of RBCs, the anaemia is typically characterised by normal RBC indices.
4. *ESKF* – is typified by uraemia and various symptoms.

CLINICAL FEATURES

Clinical features of advanced or end-stage kidney failure are listed in Table 13.

Table 13: Clinical features of advanced or end-stage kidney failure

System	*Symptoms*	*Signs*
Genitourinary	Nocturia	Proteinuria
	Thirst	Abnormal urinary sediment
Cardio-vascular	Fatigue	Hypertension
	Dyspnoea	Pericarditis
	Orthopnoea	Circulatory overload
	Chest pain	Blood volume depletion
	Oedema	
Gastro-intestinal	Anorexia	Foetor
	Nausea	Oral and buccal ulceration
	Vomiting	Parotitis
	Hiccoughs	
	Diarrhoea	
Neuromuscular	Cramps	Tremor
	Weakness	Flap (asterixis)
	Drowsiness	Hyper-reflexia going on to loss of tendon jerks
	Hallucinations	Loss of vibration sense and light touch
	Fits	
	Stupor. Coma	
Cutaneous	Itching	Dry skin
		Pigmentation
		Scratch marks
		White bands on nails
Haematological	Bruising	Anaemia
	Epistaxis	Bruises
	Dyspnoea	Microangiopathic haemolyticanaemia
	Fatigue	
	Sore eyes	Congested eyes
Ocular	Failing vision	Corneal calcification
		Retinopathy
		Retinal detachment
Skeletal	Bone pain	Deformities or rickets in children

MANAGEMENT

Indications for Initiation of Therapy in ESRD

- Hyperkalaemia resistant to medical therapy
- Metabolic acidosis resistant to medical therapy
- CKF resistant to medical therapy
- Uraemic symptoms
- Uncontrollable hypertension
- Pericarditis
- Neuropathy
- Encephalopathy
- Uraemic coagulopathy

COMPLICATIONS AND CONSEQUENCES OF CKF

Cardiovascular disease – incidence is 3–5 fold greater, and even microalbuminuria significantly increases cardiovascular risk. Explanations include high prevalence of diabetes, hypertension, dyslipidaemia and LV hypertrophy and other factors such as hyperhomocysteinaemia, increased oxidative stress, progressive malnutrition and 'micro-inflammation'.

Anaemia is common resulting from a reduction in circulating erythropoietin and some bone marrow resistance to its action. There is high chance of bleeding in these patients.

Bleeding in Uraemia

Mechanisms

1. Increased prostacyclin production by the endothelium and reduced biosynthesis of thromboxane.
2. Accumulation of waste products (urea and its metabolite guanidinosuccinic acid) in uraemic plasma may lead to smaller platelet size, reduced platelet coagulant activity (platelet factor III), decreased platelet adhesion, defects in cytoplasmic calcium mobilization, decreased expression of fibrinogen receptors and impaired platelet aggregation, and consequently prolonged bleeding time.
3. Anaemia may contribute to reduced adhesion in vivo, and consequently, abnormal bleeding time.

Renal bone disease is a composite of high and low bone turnover disease. Patients with uraemia exhibit skeletal resistance to the action of circulating parathyroid hormone, and often incipient vitamin D deficiency. Early symptoms are uncommon, so biochemical and radiological analysis are required.

Malnutrition is common, particularly as renal function deteriorates to GFR 10-20 ml/minute. Fluid retention may mask loss of muscle, so body weight may change little.

Endocrine abnormalities include dysregulation of vitamin D and lack of erythropoietin. Increased reverse free triiodothyroxine conversion is also seen. Reduced insulin degradation by renal tubules is a feature of GRF < 40 mL/minute. Testosterone levels are often low in male dialysis patients, and prolactin elevation can contribute to gynaecomastia. Erectile dysfunction is common.

Infection rates and immune system function are often abnormal. Infection is a common cause of death.

Malignancy is more common and on dialysis. This is partly explained by presence of multicystic kidneys, but increased incidence of primary liver and thyroid cancer and lymphoma are reported. This may relate to impaired immune surveillance and T cell function.

Psychiatric problems are common in CKF and dialysis patients and may range from depression, anxiety and phobias to full-blown psychosis.

Neuromuscular problems are peripheral and autonomic neuropathy. Peripheral neuropathy usually becomes clinically evident after the patient reaches stage 4 CKD. "Restless leg syndrome" is seen. It is characterized by ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement.

Dermatological complication: Apart from pruritus another complication is nephrogenic fibrosing dermopathy consists of progressive subcutaneous induration, especially on the arms and legs. The condition is similar to scleromyxedema and is seen very rarely in patients with CKD who have been exposed to the magnetic resonance contrast agent gadolinium.

Management to Retard/Prevent Progression of CKF

Blood pressure control. ACE inhibitors reduce risk of ESKF by about 30%. Calcium channel blockers when used together with ACE inhibitors/ARBs are highly effective and confer nephroprotection. BP targets of 130/80 mm Hg for all renal patients are widely accepted.

Lipid-lowering therapy with statins for all patients with cardiovascular history or diabetes.

Cardiovascular Diseases in Uraemia

Uraemic vasculopathy – Loss of vascular elasticity due to thickening of arterial wall contributes to higher systolic and lower diastolic pressure. An unusual feature of uraemic vasculopathy is the extent of calcium deposition both in intimal layer of the artery, but also in the media.

Uraemic cardiomyopathy – Severe myocardial disease may manifest as both impaired myocardial contractility which leads to both systolic and diastolic dysfunction. Clinical features are of CHF, and arrhythmias, and patients with end-stage cardiomyopathy often become hypotensive.

Possible cardiovascular risk factors in uraemia and its management are given in Table 14.

Anaemia– Factors contributing to anaemia in CKD are listed in Table 15. Anaemia of CKF is normochromic and normocytic and hypoproliferative. Reticulocyte count is inappropriately low for the degree of anaemia, but the peripheral blood film often looks normal except for occasional fragmented cells (burr cells).

Management

Erythropoietin therapy – Erythropoietin is a large glycoprotein containing 165 amino acids. Usual starting dose is 2000 units 2–3 times per week s.c. A reticulocyte response is obtained within 3–4 days, and haemoglobin concentration usually begins to increase from 2 weeks onwards. Erythropoietin therapy should be commenced once Hb concentration falls below 10g/dl, and the recommended target of Hb concentration in dialysis patients is 11–12 g/dL.

Efficacy – Erythropoietin therapy is effective in correcting the anaemia in 90-95% patients, and has secondary benefits, such as reduction in high cardiac output, increased peripheral vascular resistance, improvement in myocardial ischaemia and reduced LV mass.

Side effects – Most common is hypertension. Others include an increased risk of stroke in those with type 2 diabetes and increase in thromboembolic events, perhaps a faster progression to the need for dialysis, thrombosis of vascular access, clotting of dialysis lines, hyperkalaemia, flu-like symptoms and skin irritation around injection site. A serious side effect reported is red cell aplasia with anti-erythropoietin antibodies.

Darbepoetin alpha is a second generation erythropoietic agent which has longer circulating half-life, and hence has to be given less frequently (once weekly or every other week). The conversion factor is about 200 units of erythropoietin to 1µg of darbepoetin alpha.

Epoetin beta can be self-administered s.c. by the patient by use of a pen. Dose 3 × 20 IU/kg body wt/week initially. May be increased every 4 weeks, but maximum dose should not exceed 720/IU/kg week.

Renal osteodystrophy – The term generally encompasses four major histological types of bone disease:

- Secondary hyperparathyroidism
- Osteomalacia
- Mixed renal osteodystrophy
- Adynamic bone disease

Biochemical disturbances and radiological features of renal osteodystrophy are listed in Table 16.

Other skeletal complications of renal failure include osteoporosis, dialysis-associated amyloid and metastatic calcification. Patients with a GFR of 60 mL/minute/1.73 m^2 are at risk and should be evaluated for bone disease.

Table 14: Possible cardiovascular risk factors in uraemia and its management

Uraemic vasculopathy
• Smoking
• Diabetes mellitus
• Hypertension
• Dyslipidaemia
• Hyperhomocysteinaemia
• Increased oxidative stress
• Elevated calcium phosphate product
• Inflammation
Uraemic cardiomyopathy
• Hypertension
• Anaemia
• Volume overload
• Diabetes mellitus
• A-V fistulas
Management
• Cessation of smoking and healthy lifestyle modifications
• Treatment of hypertension
• Treatment of lipid abnormalities
• Treatment of anaemia
• Adequate glycaemic control in DM
• Control of plasma calcium and phosphate levels
• Reduction in homocysteine levels
• Antioxidant therapies
• Anti-inflammatory drugs (e.g. aspirin)

Table 15: Factors contributing to renal anaemia

• Relative deficiency of erythropoietin
• Shortened RBC survival (haemolysis or hypersplenism)
• 'Uraemic inhibitors' of erythropoiesis
• Hyperparathyroidism with marrow fibrosis
• Aluminum toxicity
• Blood loss (mainly GI tract)
• Chronic inflammation
• Iron, folate and vitamin B_{12} deficiency

Mixed renal osteodystrophy – Mineralization time can be measured by giving patients tetracycline before renal biopsy. Increased osteoid may be caused by increased production (in hyperparathyroidism) or reduced mineralization (osteomalacia). Mixed renal dystrophy is said to occur when both abnormalities are found on bone biopsy.

In addition, strong epidemiological evidence indicates an association between hyperphosphataemia and increased calcium phosphate product, and coronary artery calcification and death.

Another complication of mineral metabolism is "calciphylaxis". Calciphylaxis (calcific uremic arteriolopathy) is a devastating condition seen almost exclusively in patients with advanced CKD. It is heralded by livedo reticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen and breasts. Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. Originally it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. However, more recently, calciphylaxis has been seen with increasing frequency in the absence of severe hyperparathyroidism. Other etiologies have been suggested, including the increased use of oral calcium as a phosphate binder and warfarin, which is commonly used in hemodialysis patients and one of the effects of warfarin therapy is to decrease the vitamin K dependent regeneration of matrix GLA protein. This latter protein is important in preventing vascular calcification.

Clinical features – (a) Cutaneous manifestations – Pruritus and conjunctival calcification resulting in acute infection ('red eye' syndrome of renal failure) and rarely calciphylaxis. (b) Growth and skeletal maturation stunted in children. (c) Osteomalacia associated with bone pain, skeletal deformity and waddling gait.

Treatment – should be started early when creatinine clearance falls to about 40 mL/minute. (a) Phosphate binders – As renal failure advances, dietary reduction of phosphate may not suffice. Calcium carbonate or acetate 2–8 g/day with meals. In some patients if serum phosphate is not controlled, aluminium phosphate binders (at the lowest effective dose) must be used. Sevelamer hydrochloride (a non-absorbable polymeric phosphate binder) is a newer effective agent. (b) Suppression of PTH – Treatment with oral calcitriol should aim to maintain levels at 1.5-3 times normal. Dose ranges from 0.25 µg on alternate days to 1 µg/day. Calcitriol 'pulse therapy' in which higher doses (2–4 µg) are given three times weekly PO or IV is also effective.

Table 16: Biochemical disturbances and radiological features of renal osteodystrophy

Type of bone disease	*Biochemical features*	*Radiological characteristics*
Hyperparathyroid	Early low calcium, high-normal phosphate, raised calcium phosphate product PTH > 3 times normal Serum phosphate, alkaline phosphatase and PTH rising with increasing severity Hypercalcaemia with tertiary hyperparathyroidism	Osteopaenia and areas of sclerosis ('Rugger-Jersey spine'), 'pepper-pot skull' Subperiosteal erosions first seen in phalanges Metastatic calcification Reduced bone mineral density on DXA
Osteomalacia	Tendency to lower serum phosphate levels, more severe acidosis, lower serum calcitriol levels, low or only slightly elevated PTH Elevated serum aluminium may be the cause	Osteopaenia, Looser's zones particularly in ribs, scapulae and pelvis, skeletal deformity, vertebral compression Reduced bone density on DXA
Adynamic bone disease	Tendency to hypercalcaemia, particularly in patients given calcitriol Normal serum alkaline phosphatase Low PTH	Osteopaenia Reduced bone mineral density on DXA

Combined use of calcium salts and calcitriol increase the risk of hypercalcaemia and regular blood monitoring is required. (c) Parathyroidectomy is occasionally required.

Control of aluminium – Development of hypercalcaemia with small doses of calcitriol should suggest aluminium toxicity or adynamic bone disease. Serum aluminium levels should be checked periodically and should be less than 50 µg/L. Desferrioxamine can be used in provocative tests to determine the body burden of aluminium, and in treatment to remove aluminium by chelation.

MANAGEMENT OF END-STAGE KIDNEY FAILURE

Renal replacement therapy (RRT)

Typically renal replacement therapy is initiated in patients with creatinine clearance less than 10 mL/minute, or less optimally when uraemic symptoms are present. Dialysis attempts to replace the excretory functions of the kidney.

Haemodialysis

Principles

Diffusive and convective mass transfer across a semipermeable membrane, allowing changes in the composition of body fluids.

- Diffusive transport depends on solute molecular weight and charge, transmembrane concentration gradients, blood and dialysis flow rates and membrane characteristics. Small molecules (e.g. urea) are cleared well.
- Convection is the bulk movement of solvent and dissolved solute across the membrane, down a transmembrane hydrostatic pressure gradient. Convection improves the clearance of poorly diffusible middle molecule (e.g. b_2 microglobulin). Ultrafiltration is convective movement of water across the membrane.

Haemodialysis techniques

- Conventional haemodialysis uses low-flux, regenerated cellulose dialysers, allowing diffusive but little convective solute removal. Middle molecule clearance is poor.
- Haemofiltration is a convective treatment. Clearance of middle molecules is greatly improved, but that of small molecules is poor. This technique is unsuitable for maintenance therapy of ERKF.
- High flux haemodialysis uses biocompatible membranes with high ultrafiltration coefficients, allowing convective and diffusive solute removal.
- Haemodiafiltration adds a greater convective component to high-flux haemodialysis. Middle molecule clearance is excellent.

Managing Dialysis

Adequate dialysis and duration – Optimal dialysis dose is defined in terms of normalized urea clearance, Kt/V (where K is the dialyser urea clearance duration of dialysis in minutes, and V the urea distribution volume estimated as total body water from anthropomorphic data). Kt/V of > 1.05 or > 1.2 per session is a minimum threshold for well-nourished patients dialysed three times per week.

Vascular access – Obtaining and maintaining reliable venous access monitoring can pre-empt problems. Fistula flow assessment by ultrasound is probably the method of choice.

Acute Complications

- Dialysis disequilibrium syndrome is caused by rapid reductions in serum osmolality and paradoxical CSF acidosis, producing cerebral oedema. It presents with restlessness, headache, tremors, and occasionally, fits and coma. It occurs in severely uraemic patients subjected to over-aggressive initiation of dialysis.
- Symptomatic hypotension, causing nausea, vomiting, dizziness and syncope, is a consequence of excessive ultrafiltration, particularly in patients with cardiovascular compromise or those on anti-hypertensive medication.
- Anaphylactoid reactions occur in first 20 minutes. They may be caused by ethylene oxide sensitivity and complement activation by bio-incompatible membranes.
- Pyrexia is often caused by central venous catheter-related sepsis.
- Pyrogen reactions are uncommon if ultrapure water is used.
- Other complications (e.g. air emboli, circuit disconnection) are with modern fail-safe machines.

Dialysis-related amyloidosis usually presents as carpal tunnel syndrome and destructive arthropathy. Amyloid deposits contain b_2-microglobulin which is renally excreted, accumulates in patients with ESKF, and is not cleared by low-flux membranes.

Other chronic complications – Anaemia is largely attributed to erythropoietin deficiency, though repeated blood loss and, in high flux treatments, vitamin B_{12} and folate loss may contribute. Phosphate retention (often aggravated by short dialysis duration), hypocalcaemia and deficiency of calcitriol contribute to secondary hyperparathyroidism.

Peritoneal Dialysis

Peritoneal dialysis is a form of renal replacement therapy which enables removal of nitrogenous waste products from the body, using peritoneal dialysis fluid (PDF) instilled via a catheter into the peritoneal cavity.

Peritoneal Dialysis Regimens

Continuous ambulatory peritoneal dialysis (CAPD) uses the smallest volume of dialysate possible to prevent uraemia (8–10 litres daily) with four daily exchanges of 0.5–3.0 litres.

Automated peritoneal dialysis refers to all forms of peritoneal dialysis using a mechanical device (cycler) to assist in the delivery and drainage of dialysate. Regimens are – (a) continuous cyclic peritoneal dialysis, (b) nightly intermittent peritoneal dialysis, and (c) tidal peritoneal dialysis. Main advantage of automated peritoneal dialysis is that it eliminates the need for intensive manual involvement. Most dialysis occurs at night during sleep. However,

daytime exchanges may be necessary to achieve solute and fluid removal targets.

Advantages and Disadvantages of Peritoneal Dialysis

Advantages of peritoneal dialysis over haemodialysis:

- Peritoneal dialysis is a technically simple procedure. Hence, it can be safely performed at home or at work by patients who have completed a brief training course. Little or no special equipment is required.
- Peritoneal dialysis provides continuous excretory function with steady-state biochemistry. Therefore, patients experience few of the cyclical symptoms associated with haemodialysis-induced fluid and electrolyte shifts.

Disadvantages

- Peritoneal dialysis is less efficient than haemodialysis, and adequate excretory function often depends on patient's residual renal function.
- The presence of peritoneal dialysis catheters may cause body image or psychosexual problems.
- Successful peritoneal dialysis relies on the efficiency of the peritoneal membrane, which is often damaged by peritonitis, thereby rendering it technically impossible.

Medical Contraindications to Peritoneal Dialysis

Relative

- Large muscle mass – potentially inadequate dialysis
- Obesity – difficulty with catheter insertion
- Intestinal disease – potential to initiate peritonitis
- Respiratory disease – intolerance of splinting of diaphragm by intraperitoneal fluid
- Hernia – exacerbated by peritoneal dialysis fluid if not surgically correctable

Absolute

- Abdominal wall stoma – high risk of peritonitis
- Diaphragmatic fluid leak – peritoneal fluid leak causes pleural effusions
- Adhesions – hinder flow of peritoneal dialysis fluid
- Loss of peritoneal function or integrity – peritoneal dialysis not technically possible

Complications of Peritoneal Dialysis

Infection may occur anywhere along the dialysis catheter. Peritonitis is the major infective complication; it is diagnosed by the combination of abdominal pain and/or cloudy PDF effluent with a WBC count > 100/μL.

Non-infectious complications

- Loss of ultrafiltration despite high concentration of glucose in the PDF
- Drainage problems caused by catheter migration (constipation is the most common cause)
- Fluid leaks into external genitalia, pleural space or abdominal wall
- Abdominal or back pain and exacerbation of abdominal wall hernias (caused by the presence of PDF).

KIDNEY TRANSPLANTATION

Kidney transplantation is the treatment of choice for ESKF, as it enables the patient to resume a normal life, with no restrictions in diet and fluid intake.

Pre-Transplantation Assessment

Donor

Cadaver – Patients with maintained cardiac output in whom the criteria for brainstem death have been met. Donor characteristics that preclude transplantation include: Malignancy, sepsis, infection with hepatitis B or C virus or HIV, irreversible renal impairment.

Live – Living-related transplantation results in better graft outcome. Normal renal function in the donor is a prerequisite, and transplantation of a kidney with a single large artery is preferable.

Recipient

Non-immunological

Vascular disease – Cardiovascular disease is the most common cause of death in both the dialysis and transplant populations. Diabetes is a common cause of ESKF. Other risk factors, such as hypertension, hypercholesterolaemia, smoking and obesity should be identified and treated. Extent of peripheral vascular disease should be ascertained.

Malignancy – Patients with history of malignancy should have been in remission for at least 2 years before transplantation is considered.

Infection – There should be no evidence of active sepsis. HIV infection is a contraindication because prognosis of HIV-positive patients on immunosuppression is poor.

Recurrent renal disease – Focal segmental glomerulosclerosis often recurs, with early graft loss. Diabetic and IgA nephropathy also commonly recurs, but seldom causes renal insufficiency.

Immunological – The human leucocyte antigens (HLA) are important in antigen presentation to T cells. Variation

in these proteins between individuals results in the graft being seen as 'foreign' by the immune system, resulting in rejection. HLA of donors and recipients enables assessment of their compatibility.

Immunosuppression

Glucocorticoids – After transplantation, the dose is tapered to maintenance level of 5–10 mg/day. High-dose IV corticosteroids are used in treatment of acute rejection.

Azathioprine inhibits purine metabolism and, therefore, cellular proliferation. It is used to prevent, rather than treat rejection.

Mycophenolate mofetil also blocks purine metabolism. It is more potent than azathioprine, and is used in maintenance regimens or for post-rejection rescue. GI symptoms are more common than with azathioprine.

Cyclosporine binds to and inhibits calcineurin. This blocks part of the signalling cascade responsible for lymphocyte activation. It has a narrow therapeutic window and nephrotoxicity is a major problem.

Tacrolimus also inhibits calcineurin. It is more potent than cyclosporine and therefore used as both rescue agent for treating rejection and a maintenance agent. Side-effects are similar to those of cyclosporine.

Sirolimus is synergistic with cyclosporine, but is not nephrotoxic.

Antibodies, both polyclonal (ALG and ATG) and monoclonal (OKT3), and anti-T cell antibodies are used in treatment of acute rejection refractory to corticosteroids. Their administration is commonly associated with cytokine release syndrome. Subsequent risk of opportunistic infections and lymphoid malignancies is increased. Anti-CD25 antibodies (daclizumab and basiliximab) target activated T cells only and, therefore, have few side-effects. They are used to prevent rejection in the early post-operative period. Belatacept is a fusion protein that binds costimulatory ligands (CD80 and CD86) present on antigen-presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T cell anergy and apoptosis. Belatacept is FDA approved for kidney transplant recipients and is given monthly as an intravenous infusion.

Complications

Immediate

ATN is the most common cause of immediate graft dysfunction. Kidneys from older donors and those who are hypotensive are more likely to develop ATN.

Surgical complications include renal venous and arterial thrombosis.

Hyperacute rejection results from presence of pre-existing antibodies. There is no effective treatment except graft nephrectomy.

Early

Immunological – Acute rejection is seen in 30–60% and usually presents as decline in renal function in first few months. Renal biopsy confirms the diagnosis, assesses severity of rejection and guides treatment.

Infection – CMV infection develops in weeks or months in 60% of CMV-seronegative recipients receiving grafts from seropositive donor, unless prophylaxis with ganciclovir or valaciclovir is given.

Post-transplantation lymphoproliferative disorders – These EB virus-related malignancies are more common in patients who have received antibody therapy on induction and in children.

Mechanical – Arterial and ureteric stenoses with gradually deteriorating renal function.

Late

Chronic rejection is the most common cause of late graft failure. The process is influenced by immunological and non-immunological factors.

Malignancy is three times more common, e.g. squamous cell skin carcinoma, renal, cervical and vaginal cancers.

Cardiovascular disease is the principal cause of death post transplantation

Recurrent disease is mentioned earlier.

Drug Effects

Rapidly Progressive Kidney Failure

Rapidly progressive renal failure (RPRF) is an initial presentation in patients who present with progressive renal impairment of short duration. The underlying aetiology may be a primary renal disease or a systemic disorder (Table 17).

Clinical Features

(i) Since anaemia is one of the important features of CKD, absence of pallor is one of the signs. (ii) Hypertension if underlying thrombotic microangiopathy and renal artery stenosis. (iii) Oral ulcer or butterfly rash suggests lupus. (iv) Skin petechiae may indicate lupus vasculitis.

Investigations

(i) Ultrasound of abdomen – Presence of normal-sized kidney. (ii) Urine – Active urinary sediment (proteinuria, dysmorphic RBCs and RBC casts) suggests proliferative GN.

Hematuria with isomorphic RBCs is indicative of acute interstitial nephritis. (iii) Kidney biopsy – Crescentic GN is one of the most important causes of RPRF, acute tubular necrosis, acute interstitial nephritis.

Treatment

Since the causes of RPKF are heterogenous, the treatment is varied. Vasculitis and lupus nephritis need prompt immunosuppression, sometimes with plasmapheresis, chemotherapy for multiple myeloma, etc.

6. URINARY TRACT INFECTION (UTI)

UTI is the presence of microbial pathogens in the normally sterile urinary tract. UTI can be either symptomatic or asymptomatic.

Uncomplicated and complicated infections – Uncomplicated UTI occurs in healthy women. Complicated UTI is associated with anatomical, functional, or metabolic abnormalities of the urinary tract that disable the natural innate host defences and lead to tissue injury. Factors associated with UTI are listed in Table 18.

Cystitis is inflammation of the bladder. Infection is the most common cause, but there are other non-bacterial causes (Table 19).

Aetiology of UTI – Bacteria most commonly enter the urethra (ascending infection) but can enter via the blood stream. Ascending infections account for most cases of uncomplicated cystitis and pyelonephritis, and usually involve organisms of normal bowel flora – *E. coli. Staph. saprophyticus* is sometimes found in young women, and *Proteus mirabilis* and *Klebsiella pneumoniae* are rare causes. Predisposing factors have been tabulated earlier.

Table 17: Causes of rapidly progressive kidney failure

Primary renal disease
Antineutrophil cytoplasm antibody-associated vasculitis
Antiglomerular basement disease
(Good pastures disease)
Lupus nephritis
Crescent phase of primary GN
(e.g. IgA nephropathy)
Post-infectious GN
Cryoglobulinaemic GN
Acute interstitial nephritis
Systemic disease
SLE
Multiple myeloma
Thrombotic microangiopathy

PATHOGENESIS

Virulence of an organism is related to its ability to adhere to epithelial cells, e.g. *E. coli.* The bacterium has many

Table 18: Factors associated with UTI

Uncomplicated urinary tract infection
• Bacterial virulence
• Host defence
– Colonization of vagina and mucosa
– Polymorphisms of genes regulating complement, neutrophil biology
– Non-secretor status
• Acquired (disruption of host defence)
• Anti-microbials (loss of commensal population)
• Sexual intercourse
• Ageing (post-menopausal oestrogen decrease, loss of detrusor power)
Complicated urinary tract infection
Outflow obstruction
• Urethral stricture
• Pelviureteric junction
• Prostatic hypertrophy
• Ureteric stricture
• Bladder neck obstruction
• Stone/tumours
• Neuropathic bladder
• Renal cysts
Abnormal kidney
• Renal scarring
• Vesicoureteric reflux
• Dysplastic kidney
• Duplex kidney
Foreign body
• Indwelling catheter
• Stone
• Nephrostomy tube
• Ureteric stent
• Tumour
Metabolic
• Immunosuppression
• Kidney failure
• Diabetes mellitus
• Alcoholism
• Pregnancy
• Iron overload
Other
• Enterocystoplasty
• Bladder diverticuli
• Ileal conduit
• Instrumentation

Table 19: Causes of 'culture-negative' cystitis

Infection
• Treated urinary tract infection
• Mycobacterium spp.
• Fastidious organisms
• *Schistosoma haematobium*
• *Candida spp.*
• BK polyomavirus
• Adenovirus
Inflammation
• Cyclophosphamide
• NSAIDs
• Danazol
• Bladder stone
• Pelvic irritation
Cancer
Idiopathic
• Interstitial cystitis

projecting hair-like structures (pilli or fimbriae) that interact with glycoprotein and glycolipid receptors on host cells.

INNATE HOST DEFENCE

Neutrophils are principally protective when released into the urinary tract to kill bacteria. It is only when this response is exaggerated or incomplete that neutrophils cause tissue injury.

Complement – Bacterial killing also involves complement and is enhanced by local epithelial production of IgA antibody against bacterial surfaces (acquired immunity).

Urine osmolality and pH – The survival of microorganisms is reduced in normal urine by an osmolality of 88 mOmmol/kg and pH above or below 5–7.

Colonization of distal urethra and periurethral region by anaerobic and micro-aerophilic bacteria, such as *Staph. epidermidis,* lactobacilli, corynebacteria, streptococci and *Bacteroides spp.* is a major component of normal host defence. The commensal colonies can be disrupted by antibiotic therapy and spermicidal creams, allowing virulent *E. coli* to adhere and ascend.

Bacterial washout by urine flow and bladder emptying is a major defence mechanism. Any process causing stasis of urine can lead to infection.

Uroepithelium – The uroepithelium is covered by urinary mucus and a glycocalyx that contains mannosylated proteins. These constituents bind bacteria and aid their elimination.

Blood group antigens – Women with a history of recurrent UTI are three to four times more likely to be non-secretors of ABH blood group antigens than other women.

Acquired host defence. There is no evidence that cell-mediated immunity has a role in UTI. Urinary antibodies (IgG and secretory IgA) are formed against O and K serotypes, and a systemic antibody response to O antigens occurs in pyelonephritis. Antibody binding to bacteria also aids in their elimination.

CLINICAL SYNDROMES OF UTI

Acute cystitis is associated with frequency, urgency and dysuria. Urine appears hazy and may be offensive. Microscopic hematuria is often present. There is no pyrexia.

Acute urethritis is associated with dysuria and urethral discharge. Infection is usually sexually transmitted and is caused by *Neisseria gonorrhoea* or non-gonococcal organisms including *Chlamydia trachomatis, Mycoplasma genitalium* and *Ureaplasma urealyticum.* The latter infections (non-specific urethritis) are often asymptomatic, and the organisms become permanent commensals.

Asymptomatic UTI Significant bacteriuria is often not associated with symptoms and does not require treatment except in pregnant women, in infants and before urological surgery.

Urethral syndrome – In 50% of women presenting with dysuria and frequency, bacterial counts are $< 10^5$/mL or the urine is sterile. The term 'urethral syndrome' is used in those with recurrent symptoms that have not responded to antibiotics. It is a diagnosis of exclusion. The cause of urethral syndrome is unknown.

Vaginitis (*candida, trichomonas,* non-specific) is the cause in one-third of patients, and acute urethritis and genital herpes simplex must be excluded.

Chronic and idiopathic cystitis. Chronic cystitis with pyuria and 'sterile' urine cultures is highly suggestive of tuberculous infection (Table 20). Urine must be cultured for *M. tuberculosis.* Other diagnoses must be excluded, and urine cytology, cystoscopy and bladder biopsy are required.

A diagnosis of 'idiopathic interstitial cystitis' may be reached by exclusion. This is a severe, progressive, disabling form of cystitis that often can be relieved only by cystectomy.

Prostatitis. Bacterial prostatitis may be acute or chronic. Acute bacterial prostatitis is characterized by fever, malaise, perineal pain, urgency, frequency and dysuria. Diagnosis is usually made by urine culture.

Chronic prostatitis is a cause of recurrent UTI, particularly in those in whom IVU is normal or recurrent epididymitis is present. Patients may be asymptomatic or may suffer perineal, genital or lower back pain or discomfort on voiding.

Acute pyelonephritis is associated with fever, malaise, loin pain (which may be bilateral), bacteriuria and pyuria. There may be symptoms of cystitis. The condition can present as Gram-negative septicaemia. It can be bilateral, but CT usually shows that areas of inflammation are focal. Patients are commonly febrile and CRP is raised. Patients with an abnormal urinary tract and recurrent episodes of pyelonephritis may simply complain of general malaise, headache, loss of appetite and backache and the urine is discoloured and with an offensive odour.

Rarely there is diffuse infection causing acute renal failure. This is generally seen in alcoholics, diabetics and those receiving immunosuppression. Septicaemia (usually *Staph. aureus*) can lead to micro-abscess formation in the kidney. Occasionally with very severe infection or diabetes, papillary necrosis occurs. Rarely, subacute or chronic infection develops and an abscess may extend to form a mass (renal carbuncle), or point through the capsule of the kidney to form a perinephric abscess.

COMPLICATED UTI

Chronic pyelonephritis (reflux nephropathy) – Vesicoureteric reflux, with or without infection, can cause scarring of the kidney that varies with the degree of reflux. Much of the scarring occurs in the foetal or neonatal period. Further scarring in childhood is associated with untreated UTI. Primary vesicoureteric reflux is recognized as a common inherited disease (autosomal dominant).

Progressive loss of renal function can occur in the absence of both UTI and reflux, but only in those with GFR of less than 50 mL/minute/1.73 m^2. It is invariably associated with the onset of progressive proteinuria and hypertension. This condition is now termed 'reflux nephropathy' and is associated with hyperfiltration (glomerular capillary hypertension) of the remaining glomeruli.

Chronic infections of the kidney – Complete obstruction may lead to severe infection in the renal pelvis (pyonephrosis) and loss of kidney. Obstruction with stone disease may be associated with chronic xantho-granulomatous pyelonephritis. Melakoplakia is a rare chronic infection of the kidney that presents as renal mass, and results from inability of macrophages to kill *E. coli.*

Table 20: Infections causing UTI with sterile pyuria

Chlamydia trachomatis
Mycoplasma hominis
Ureaplasma urealyticum
Mycobacterium spp.
Haemophilus influenzae
Campylobacter spp.
Legionella pneumophilia
Salmonella spp.
Shigella spp.
Gardnerella vaginalis

1. Ultrasonography of kidney and bladder and plain abdominal radiography to exclude stones and lumbosacral defects.
2. Technetium 99 m-DMSA scan in case of pyelonephritis.
3. Urine flow rate and post-void ultrasonography of bladder (to measure residual volume) in any patient with evidence of bladder outflow obstruction.
4. CT with contrast to exclude abscess if renal symptoms persist.
5. Micturating cystourethrography (MCU) in children under 1 year of age once the urine is sterile. Children aged 1–7 years should undergo MCU when initial investigations reveal an abnormality, or when there is history of pyelonephritis or recurrent UTI or family history of reflux.
6. IV pyelography gives important anatomical information about the urinary tract (calyces, pelvis and ureter), provided renal function is normal.
7. MSU in patients with pyelonephritis or complicated UTI.
8. A leucocyte esterase dipstick can be used to detect pyuria and dipsticks can detect nitrite (produced by bacterial metabolism of urinary nitrate).

MANAGEMENT OF UTI

General measures – More fluid intake, alkalization of urine with potassium citrate solution to alleviate symptoms.

Antibiotics

Acute cystitis. Empirical 3-day regimens of trimethoprim, oral cephalosporin or nitrofurantoin. Ciprofloxacin is also effective, but should not be used as first-line (to prevent development of resistance). Recurrent infection may be due to – Persistent focus of infection, relapsing infection

with the same organism, re-infection with a different organism. Persisting or relapsing infection may require a 6-9 month's course of prophylactic antibiotics. Re-infection may require pericoital prophylaxis.

Acute pyelonephritis – Oral therapy with a quinolone for 7 days is usually sufficient. More sick patients (nausea, vomiting, hypotension or sepsis) may require hospitalization for initial parenteral therapy (once-daily aminoglycoside plus quinolone, or a third-generation cephalosporin or Tazocin), for first 1–3 days followed by appropriate oral therapy for up to 14 days.

Prostatitis – Lipid-soluble antibiotics (trimethoprim, doxycycline, quinolones) which penetrate tissues given for 2-4 weeks.

Antibiotic resistance – The concentration of antibiotic used to test bacterial sensitivity in the laboratory (mean inhibitory concentration) is often well below the concentration of antibiotic achieved in the urine. Thus, the organism may respond to an antibiotic despite that the microbiologist-reported resistance.

Prevention – (a) Those with residual urine after voiding should practise double micturition. (b) UTI associated with sexual intercourse may benefit from emptying of bladder afterwards, or from taking prophylactic dose of antibiotic at the time of intercourse. Vaginal oestrogen creams are effective in post-menopausal women.

Management of abnormal bladder, enterocystoplasty and conduits – Long-term antibiotics to eradicate infection from kidneys. Tetracycline and oxytetracycline are contraindicated because they are toxic to damaged tubules. Doxycycline can be used. Nitrofurantoin and nalidixic acid are avoided in patients with GFR < 50 ml/minute, because they are renally excreted and toxic in renal failure. Quinolones are not to be used as regular prophylactic antibiotic, because of risk of inducing resistance. Attempts to sterilize the urinary tract are unlikely to be successful when foreign bodies such as stones remain.

Catheter-associated UTI is the most common nosocomial infection. Bacteriuria develops in 1–2% of healthy patients following catheterization, and the risk of infection increases with duration. Microbes become embedded in a biofilm and are much less susceptible to antibiotics.

Bacteriuria in pregnancy. Asymptomatic bacteriuria may be found in a few pregnant women and is associated with premature delivery and low birth weight. Pyelonephritis develops in 30-40% with untreated bacteriuria.

UTI in children. UTI occurs predominantly in boys in the first 2–3 months of life and equally in boys and girls at 3–12 months. After 1 year, UTI in boys becomes increasingly rare.

In infants, symptoms are usually nonspecific and include feeding disorders, slow wt. gain, vomiting and diarrhoea. Neonates may present with shock and septicaemia. In children, malaise and fever with abdominal pain arouse suspicion of UTI.

Indications for Urine Culture in Children

- Infant at home with unexplained rectal temperature > 38.5°C
- Any child admitted to hospital with pyrexia
- Unexplained vomiting or abdominal pain
- Frequency of micturition, dysuria or enuresis
- Failure to thrive
- Prolonged jaundice in the newborn
- Hematuria or hypertension
- Nonspecific illness
- Suspected sexual abuse

Investigations in UTI for the following patients:

- All children
- Women with recurrent UTI
- Men who do not respond to single course of antibiotics
- All patients with pyelonephritis

7. POLYCYSTIC DISEASE OF KIDNEYS

Inherited kidney disorder characterized by multiple bilateral cysts that cause enlargement of the kidney and reduce, by compression, the functioning renal tissue.

Table 21 lists various inherited kidney disorders.

The two major genes in autosomal dominant polycystic kidney disease (PDK1 and PDK2) have been identified.

Table 21: Inherited kidney disorders

• Cystic kidney diseases
• Airport's syndrome and variants
• Metabolic diseases with kidney involvement (e.g. Anderson-Fabry disease, cystinosis)
• Tubular disorders
• Diseases with nephrolithiasis (e.g. primary hyperoxaluria)
• Syndromes with renal and extrarenal involvement Nail-patella syn. – nail and bone abnormalities with patella defects and abnormalities of kidneys.
Bardet-Biedl syn.: Mental retardation, polydactyly, obesity, pigmentary retinitis, hypogenitalism and renal disease
• Primary immune GN, occasionally familial (e.g. IgA)
• Renal diseases with genetic influence (e.g. reflux nephropathy)

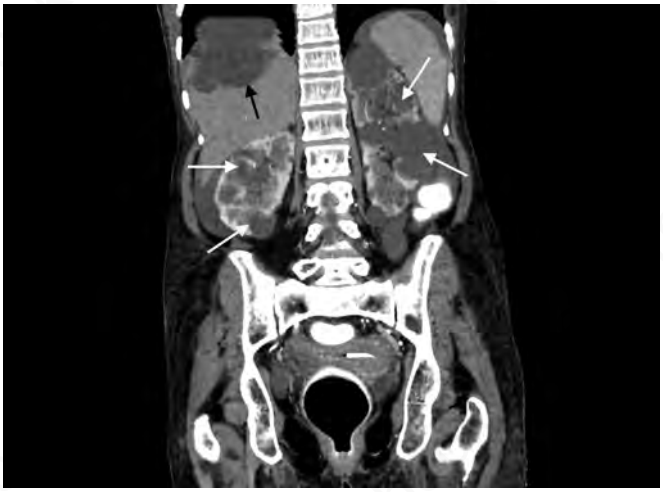


Fig. 5: CECT coronal showing polycystic kidney disease (white arrows) and hepatic cyst (black arrow).

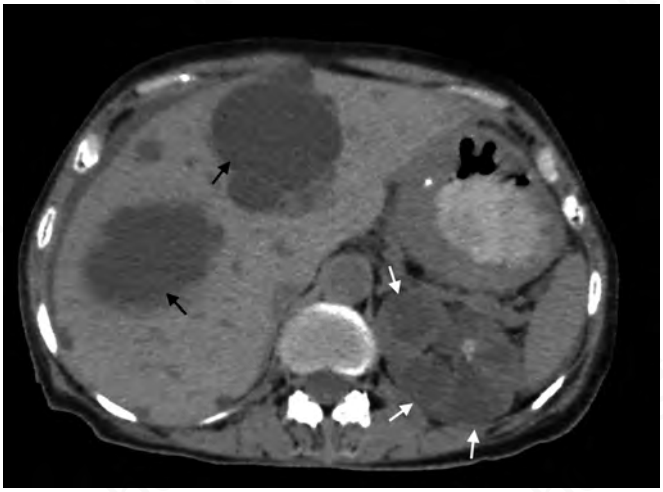


Fig. 6: CECT axial showing polycystic kidney disease (white arrows) and hepatic cyst (black arrows).

CLINICAL PRESENTATION

ADPKD can present at any age, but most commonly manifests in adults. Common presenting symptoms include hypertension, UTI, hematuria, loin pain and renal calculi (Fig. 5). Many patients present with ESKF without a preceding history.

Childhood or infantile ADPKD. Rarely, ADPKD presents in a severe form during foetal life or early childhood, and may initially be confused with autosomal recessive polycystic kidney disease, which usually presents at this age. To avoid confusion, this presentation is termed 'early-onset ADPKD'. In the absence of a positive family history, ultrasonography is useful in both parents of an affected child.

Extrarenal Manifestations

ADPKD is now recognized as a systemic disease rather than one restricted to the kidney. Cysts are commonly found in liver and pancreas (Fig. 6). Rarely hepatic cyst formation is severe (polycystic liver disease). Other non-cystic manifestations include intracranial aneurysms, mitral prolapse and colonic diverticulae. Subarachnoid hemorrhage is a devastating first presentation in some young patients.

GENETIC HETEROGENEITY

Most ADPKD families carry mutations in PKD1 (85–90%). PKD2 patients (10–15%) exhibit a milder renal cystic phenotype than PKD1, e.g. median age of onset of ESKF is 15 years later with PKD2, and incidence of hypertension, UTI with PKD1 are four to two times respectively higher than with PKD2. Genetic classification of patients as PKD1 or PKD2 is, therefore, of prognostic relevance.

TREATMENT

No specific treatment to prevent cyst growth or the decline of renal function. Blood pressure control to a target of 1 40/90 mm Hg is recommended according to the guidelines from the eighth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VIII report) for reducing cardiovascular complications in ADPKD and renal disease progression. Some clinical trials showed V2R antagonists and somatostatin analogues slow the decline of renal function, although with some side effects such as liver function impairment, polydipsia and diarrhoea.

8. TUBULO-INTERSTITIAL DISORDERS

CKF is accompanied by tubulointerstitial atrophy and fibrosis, regardless of the cause.

CLASSIFICATION

Tubulointerstitial disorders can be classified into acute interstitial nephritis (AIN) and chronic interstitial nephritis (CIN). See Table 22 for the causes of tubulointerstitial nephritis.

Chronic interstitial nephritis

- *Allergic nephropathy – phenacetin.*

Table 22: Causes of tubulointerstitial nephritis

Acute interstitial nephritis
1. **Drug-induced**
Antibiotics
• Penicillins
• Sulphonamides
• Rifampicin
• Quinolones
• Vancomycin
Non-steroidal anti-inflammatory drugs
Anticonvulsants
• Phenytoin
• Valproate
• Lamotrigine
Others
• Allopurinol
• Phenindione
• Furosemide
2. Infections
Viruses
• Hantaviridae
• E-B virus
• HIV
• Measles
• Adenovirus
Bacteria
• Legionella
• Leptospira
• M. tuberculosis
• Streptococci
• Salmonella
• Campylobacter
• Mycoplasma
• Chlamydia
• Brucella
Others
• Leishmania
• Toxoplasma
Immunocompromised
• Polyomavirus
• CMV
• Herpes simplex virus
Contd...

Contd...
3. **Multisystem inflammatory disorders**
• Sarcoidosis
• Sjogren's syndrome
• SLE (rarely)
• Granulomatous polyangiitis
• TIN with uveitis
• IgG4- related systemic diseases
4. **Acute obstructive disorders**
Light chain cast nephropathy ("myeloma kidney)
Acute phosphate nephropathy
Acute urate nephropathy

- *Lithium toxicity*
- *Heavy-metal intoxication*
- *Radiation nephritis*
- *Calcinuria inhibitor toxicity*
- *Eating disorders*
- Idiosyncratic drug reactions, infections and multisystem inflammatory disorders
- Vesicoureteric reflux disease
- Sickle cell disease

CLINICAL FEATURES

The mode of presentation differs between AIN and CIN and between different causes, but predominant tubulointerstitial damage has some typical effects. Patients often present with uraemia and fluid overload, occasionally with extra-renal manifestations like fever, skin rash and arthralgia, particularly in AIN. Mild albuminuria is common, microscopic hematuria is variable. There may be defects in tubular handling of water, Na and H ions, resulting in NDI, salt-losing nephropathy and renal tubular acidosis. Hypertension is variable.

TREATMENT

It consists of correction of underlying disease, stoppage of drugs and usage of steroids. Renal replacement therapy in cases of worsening renal function not responding to therapy.

Renal tubular acidosis (RTA) disorders

These are due to abnormalities of renal tubular acidification. Defects may be:

1. *Quantitative* – as in chronic kidney failure (number of functioning nephrons too small for metabolic acid load).
2. *Qualitative* –
   (a) Proximal RTA –
      (i) Primary form rare with infant failing to thrive and grow.
      (ii) Secondary form, e.g. as result of Fanconi syndrome and following renal transplantation.
   (b) Distal RTA –
      (i) Primary in early life with failure to thrive, polyuria, dehydration.
      (ii) Secondary due to vitamin D poisoning, idiopathic hypercalcaemia, amphotericin toxicity.

9. URINARY CALCULI

Stones is the urinary tract occur when urinary chemistry results in concentrations of stone salts that exceeds the limit of metastability for that salt in solution. This most often reflects excessive excretion of one or more stone constituents, deficient inhibitory activity in urine, or simply a low urine volume resulting in excessively concentrated urine.

TYPES OF URINARY CALCULI

- Calcium oxalate stones (more than 70%). Often calcium oxalate is mixed with calcium phosphate or uric acid.
- Calcium phosphate usually occurs as apatite or brushite. Calcium phosphate crystals are readily soluble in acidic urine. Thus, presence of pure calcium phosphate stone is evidence of persistently alkaline urine, as occurs in distal renal tubular acidosis.
- Uric acid stones are radiolucent by simple abdominal radiography or IVP, but radiodense on helical CT and echogenic on ultrasonography.
- Cystine stones occur only in patients with cystinuria.
- Magnesium ammonium phosphate stones (also known as 'triple phosphate' or struvite) occur in UTI with an urease-producing organism. They can be very difficult to eradicate because the organisms can infect the stone matrix, where they may be sheltered from exposure to antibiotics. Cystine stones can be resistant to lithotripsy.
- Both cystine and struvite stones can grow to fill the entire renal pelvis, forming a staghorn calculus. Staghorns are uncommon with calcium and uric acid stones.
- Rarely drugs, such as triamterene, 5-fluorocytosine and indinavir can crystallise in the urine to form stones.
- Other rare type of stones include xanthine, 2,8-dihydroxy-adenine, gypsum and silicate.

PREDISPOSING FACTORS

Hypercalciuria, the most common risk factor for formation of calcium oxalate stones, is idiopathic hypercalciuria. This is a complex condition that reflects excessive intestinal absorption of dietary calcium, excessive resorption of bone and (rarely) a renal calcium leak. Excessive intake of animal protein can increase calcium excretion through several mechanisms, including resorption of bone to buffer the acid component of animal protein. Idiopathic hypercalciuria is often hereditary. Hypercalciuria can also occur as a secondary consequence of primary hyperthyroidism, granulomatous disease (sarcoidosis, tuberculosis) and excessive intake of vitamin D or A.

Hyperoxaluria. Extreme hyperoxaluria occurs in the rare hereditary condition, primary hyperoxaluria. Less severe hyperoxaluria is seen in intestinal malabsorption. This is because steatorrhoea allows calcium to bind to fat rather than to intestinal oxalate, allowing ingested oxalate to remain free in solution and thus more available for absorption. Mild hyperoxaluria is more common in stone patients and reflects excessive dietary intake of oxalate (nuts, beans, beets, spinach, rhubarb, strawberries). Inadequate dietary calcium intake can allow increased intestinal absorption of dietary oxalate.

Citrate forms soluble complexes with calcium and is an important inhibitor of calcium stone formation. Foods that are high in citrate are usually also high in oxalate.

Hyperuricosuria is generally metabolic in origin, though a diet high in red meat can increase urate excretion, thus promoting precipitation of uric acid.

Urinary pH is important in case of uric acid, cystine or calcium phosphate stones. Acid urine favours formation of uric acid and cystine stones. In renal tubular acidosis, urine pH never falls below 5.5, and this allows crystals of calcium phosphate to form and grow.

Low urine volume. About 10% of stone-forming patients have no identifiable risk factor other than concentrated urine due to low urine volume.

EVALUATION OF STONE RISK

In all first-time stone formers appropriate diagnostic investigations should include analysis of the composition of the retrieved stone, urine culture, and measurement of serum calcium (for primary hyperparathyroidism), bicar-

bonate (to screen for renal tubular acidosis) and creatinine, and urinalysis and measurement of pH. Examination of urine sediment is often useful in revealing crystals that can indicate the likely nature of the stone.

Patients with recurrent or bilateral stones should undergo more complete metabolic evaluation, including measurement of calcium, oxalate, citrate, uric acid, sodium and creatinine in 24–hour urine specimens. Daily excretion of creatinine is the only practical measure of whether the 24–hour collection was complete, it should be invariable in patients in a steady state, regardless of renal function, and should be about 15–20 mg/kg in women and 20–25 mg/kg in men.

PREVENTIVE THERAPY IN PATIENTS WITH STONE RISK FACTORS

Fluid intake should be high to avoid periods when urine is concentrated, even at night.

Dietary calcium. In patients with hypercalciuria, a calcium intake of 800–1000 mg/day to reduce risk of bone demineralization. No dietary calcium restriction for hypercalciuria.

Sodium is an important determinant of excretion of calcium and in hypercalciuric patients, sodium intake should be not more than 2 g/day. This is important in those treated with thiazide diuretics – a high salt intake here increases risk of hypokalaemia, which can promote hypocitraturia. Another reason to restrict sodium is that natriuresis promotes urinary excretion of oxalate and uric acid.

Dietary protein. In patients with hypercalciuria in whom excessive intake of animal protein is suspected (dietary history or excessive 24-hour excretion of sulphate), less dietary protein can reduce calcium excretion.

Thiazide diuretics (chlorthalidone, indapamide) stimulate renal calcium reabsorption and reduce urinary calcium excretion.

Oxalate. Patients with hyperoxaluria should restrict intake of the many sources of oxalate.

Hypocitraturia. Potassium citrate is preferred over sodium because the former promotes citrate excretion and for the need to restrict sodium for reasons already mentioned.

Hyperuricosuria. Allopurinol 100 mg/day. Urine should be maintained alkaline in case of uric acid or cystine stones using potassium citrate or acetazolamide.

Cystinuria. Chelating agents, e.g. penicillamine and tiopronin are effective in reducing stone formation, but have various side effects. Urinary alkalinization must be maintained at all times. In patients who can tolerate such a regimen, cystine stones can even be dissolved.

SYMPTOMS

1. *Pain* – (a) *Ureteric colic* – Cramping, sharp, often excruciating pain, fluctuating in intensity but not completely remitting. Associated vomiting and sweating. Pain extends from loin down the line of ureter to groin with radiation to testes in men and labia majora or ovaries in women.
   (b) *Loin pain* – independent of ureteric colic or infection.
2. *Haematuria* – accompanying the colic or even frank haematuria in absence of colic.

SIGNS

1. *Loin tenderness* – is usually manifestation of associated infection.
2. *Palpable kidney* in the presence of staghorn calculus, or when obstruction has remitted.

COMPLICATIONS

1. *Impaction and obstruction* – most likely to occur at pelviureteric junction or in the ureter, either at the level where it crosses the common iliac vessels or where it is about to enter the bladder.
2. *Infection* – pyelonephritis, periureteritis, cystitis.
3. *Stricture of ureter*.
4. *Malignant change* – due to chronic irritation of renal pelvis by calculi.
5. *Anuria* – from obstruction of both ureters, or of a solitary ureter and kidney.

10. INCONTINENCE OF URINE

Incontinence is involuntary loss of urine.

Causes and Clinical Features

In women neurologically intact

Sphincter weakness (stress incontinence) – It is the most common cause. Although it usually occurs for the first time during pregnancy or after vaginal delivery, it may affect multiparous women with weakness of support to the urethra, after pelvic surgery or postmenopausal atrophy. It is exacerbated by increase in intra-abdominal pressure caused by a tumour, chronic cough or constipation. Patient invariably complains of symptoms of urinary leakage associated with physical exertion or on coughing.

Detrusor instability – The term describes uncontrolled spontaneous detrusor contractions. Such contractions occur during the filling phase of the micturition cycle and may be mild or severe, leading to extreme urgency and urine loss (*urge incontinence)* if the sphincter mechanism cannot be controlled adequately. Although such contractions are often spontaneous, they may be triggered by coughing, sneezing, or change of posture. The cause of this disorder in otherwise healthy women is not known.

Mixed stress incontinence and detrusor instability – It is common and may be difficult to treat because surgical treatment of stress incontinence may worsen detrusor instability.

In men neurologically intact

Detrusor instability – Incontinence is most often caused by detrusor instability which may be primary or secondary to bladder outflow obstruction.

Post-micturition dribble – It may result from weakness of bulbocavernosus muscle.

Chronic retention of urine – It implies incomplete bladder emptying with chronic bladder distension leading to urinary frequency with a dribbling overflow incontinence. Low-pressure chronic retention is caused by an acontractile detrusor, perhaps secondary to diabetes mellitus or due to ageing. High-pressure chronic retention is usually caused by bladder outflow obstruction.

Post-prostatectomy incontinence – It is usually caused by residual detrusor instability but may result from damage to the external urethral sphincter.

Neuropathic bladder – Neurological conditions causing incontinence:

- Multiple sclerosis
- Parkinson's disease and multiple system atrophy
- Cerebrovascular disease
- Spinal bifida
- Spinal cord injury/tumours
- *Disc prolapse*: Cervical, thoracic and lumbar

INVESTIGATIONS

Initial investigations

- Urinalysis for glucose, protein and hematuria
- Mid-stream urine sample for microscopy, cultures and sensitivity, and RBCs
- Blood chemistry for renal function, and prostate specific antigen in men, if indicated.

Further investigations

Urodynamic investigations

- *Measurement of urinary flow rate* – may indicate bladder outflow obstruction, detrusor instability, detrusor failure or urethral stricture on the basis of peak urinary flow, shape of the curve and duration and pattern of voiding.
- *Ultrasound examination of residual urine* (which may be high in bladder outflow obstruction) is often performed with flow rate measurement.
- *Filling and voiding cystometry* – measuring detrusor pressure on filling the bladder and urinary flow rate during voiding. This may define detrusor instability.
- *Video-urodynamic studies* – comprise cystometry and radiological visualization of the bladder and urethra and with radiopaque fluid during filling and voiding. These studies are performed to evaluate behaviour of a neurogenic bladder or to investigate incontinence following failed surgical treatment.
- *Ambulatory urodynamic studies* – are performed over several hours of natural bladder filling and are used when conventional cystometry has failed to detect a urodynamic diagnosis, and may detect detrusor instability not shown in conventional urodynamics.

TREATMENT

Female incontinence – Factors to be looked into are obesity, smoking, excessively high or low fluid intake, atrophic vaginitis, and physical disability (e.g. arthritis). Constipation may precipitate urge or overflow incontinence by compression of bladder or urethra Physiotherapy and biofeedback help. Drug therapy – Oxybutynin 2.5–5 mg t.d.s. may be helpful in detrusor instability, because of side-effects, initial dose should be low.

Male incontinence

Neurologically intact – (a) Post-micturition dribble – Patient must empty bulbar urethra by massage. (b) Primary detrusor instability – Attention to fluidintake, and anticholinergic drugs. (c) Secondary detrusor instability – For bladder outflow obstruction adrenergic antagonist, tamsulosin or prostatectomy. (d) Post-micturition dribble – Compression of bladder by patient after voiding. (e) Chronic retention of urine – Relief of bladder obstruction. (f) Post-prostatectomy incontinence caused by damage to external urethral sphincter is best treated with an artificial urinary sphincter.

Neuropathic bladder – Combinations of treatment are often required including anticholinergic agents or adrenoreceptor antagonists, CISC, cystoplasty, penile appliance perhaps preceded by external sphincterotomy, urinary diversion.

11. KIDNEY IN SYSTEMIC DISEASE

The kidneys are often affected in acquired or inherited multisystem diseases.

Diabetes. Diabetic nephropathy is defined as the appearance of persistent 'clinical' albuminuria (albumin excretion rate > 300 mg/24 hours) in an individual who has had diabetes for more than 5 years and who has concomitant retinopathy, in absence of UTI, other renal diseases and heart failure.

Mechanisms of kidney damage in diabetes mellitus are listed in Table 23.

Systemic lupus erythematosus – Presentation of renal disease varies and includes subclinical proteinuria with or without microscopic hematuria, overt nephrotic syndrome with progressive renal impairment, which is often gradual but may present as rapidly progressive glomerulonephritis.

SYSTEMIC VASCULITIS

Medium vessel vasculitis – Polyarteritis nodosa. Renal manifestation is of progressive renal impairment caused by ongoing renal infarction (Fig. 7) and hypertension.

Small vessel vasculitides are associated with hematuria, proteinuria and RBC casts indicating glomerular inflammation, in the form of necrotizing GN.

ANCA-associated diseases:

Granulomatous polyangiitis – Renal vasculitis produces fibrinoid necrosis and focal segmental GN with crescent formation and there is presence of noncaseating granuloma.

Microscopic polyangiitis – Glomerular pathology is indistinguishable from Wegener's apart from absence of noncaseating granuloma.

Table 23: Mechanism of kidney damage in diabetes mellitus

1. Diffuse glomerulosclerosis within some cases of nodular glomerulosclerosis.
2. Pyelonephritis.
3. Necrotizing papillitis.
4. Atherosclerosis of renal vessels

Churg-Strauss vasculitis – Necrotizing and/or crescentic GN can occur though less severe.

Cryoglobulinaemic vasculitis – Type II causes vasculitis and immune complex GN, often with crescent formation.

Henoch-Schonlein purpura – Renal disease is more severe in adults. Histopathology is that of IgA nephropathy, showing diffuse proliferation of mesangial cells and matrix, mesangial IgA and complement deposits.

RA – Glomerulonephritis or renal vasculitis can occasionally complicate RA.

PARAPROTEIN-RELATED DISEASES

Myeloma – Characteristic lesion in the kidney is 'fracturing' casts of paraprotein in the renal tubules, which block the tubules and cause an acute inflammatory reaction in the interstitium (which can cause irreversible renal damage). Renal dysfunction can also arise from associated hypercalcaemia (causing prerenal kidney failure or nephrocalcinosis), urate nephropathy, sepsis, AL amyloid.

AL amyloid – Deposition occurs in pre-glomerular arteries or glomeruli, resulting in nephrotic syndrome and progressive renal failure.

Haemolytic uraemic syndrome – HUS is the triad of – microangiopathic haemolyticanaemia (Coomb's test negative), thrombocytopenia and acute renal failure. These features are also seen in disseminated intravascular coagulation, but coagulation tests are usually normal in HUS.

Malignancy – Minimal-change nephrotic syndrome may be associated with Hodgkin's disease. Renal carcinomas are associated with AA amyloid.

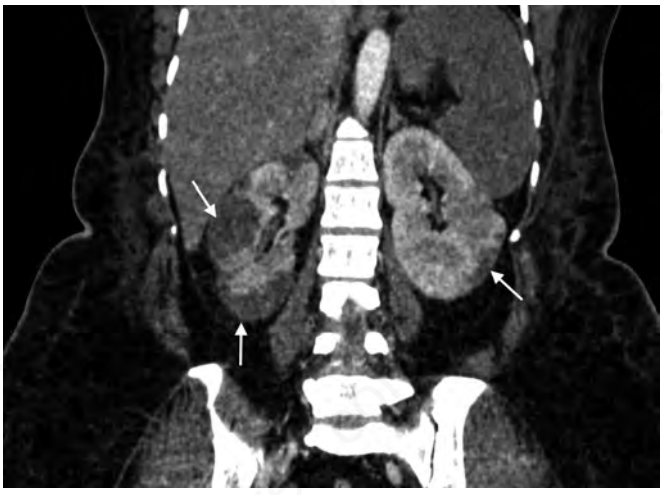


Fig. 7: Bilateral renal infarcts (arrows)

Systemic sclerosis – A syndrome of severe hypertension and acute or subacute renal failure (scleroderma renal crisis) develops in 15–20% of patients with diffuse cutaneous disease.

INFECTIONS

Systemic infections causing renal involvement are listed in Table 24.

HEPATITIS VIRUS

Hepatitis virus: HBV is associated with membranous nephropathy, usually in those infected in childhood. HVC can cause cryoglobulinaemia. Cryoglobulinaemic patients often have membranoproliferative GN, presenting with proteinuria and microscopic hematuria. Nephrotic syndrome and ESKF can develop.

OTHER CONDITIONS

At times renal disease may be associated with haemoptysis (Table 25) or jaundice (Table 26).

12. ADVERSE EFFECTS OF DRUGS ON THE KIDNEY

Drugs can cause renal damage or insufficiency by:

- Sodium and water depletion (prerenal changes)
- Changes in blood supply
- Direct renal damage
- Renal obstruction

Some drugs cause renal insufficiency by more than one mechanism (Table 27).

Table 24: Systemic infections causing renal involvement

Bacterial
• Post-infection GN
• Infective endocarditis
• Leptospirosis
• Chronic bacterial sepsis and secondary amyloidosis
Viral
HIV
• HIV nephropathy: Nephrotic syndrome, and often rapid progression to ESKF
• HIV-associated haemolytic-uraemic syndrome
• Immune complex glomerulonephritis
• Renal infection: Pyelonephritis, CMV nephritis, tuberculosis
• Renal lymphoma: Non - Hodgkin's
Hantavirus: Acute interstitial nephritis

ADVERSE DRUG REACTIONS CAUSED BY INDIRECT INTERACTIONS WITH RENAL INSUFFICIENCY

Hypovolaemia causes increased sensitivity to hypotensive drugs, particularly α-receptor antagonists and ACE inhibitors.

Bleeding is more likely in patients with uraemia. The effect of anticoagulants is enhanced and aspirin and NSAIDs are more likely to produce GI bleeding.

Hyperkalaemia is often a consequence of renal insufficiency. Potassium-sparing diuretics, potassium supplements and ACE inhibitors can exacerbate this.

Nausea and vomiting can be aggravated by some drugs (e.g. theophylline).

Nephrotoxic antibiotics – With the exception of erythromycin, the antibiotics whose names end in mycin are nephrotoxic

13. RENAL DISEASE AND PREGNANCY

Patients with renal disease that is likely to progress should be advised to become pregnant early in the course of their disease. However, the following points must be considered.

Table 25: Renal failure with haemoptysis

• Goodpasture's, Wegener's, HSP, PAN, SLE, cryoglobulinaemia.
• Renal vein thrombosis with pulmonary embolism.
• Pulmonary oedema in ARF.
• Right-sided infective endocarditis with septic pulmonary emboli and immune-complex nephritis.
• Infection – TB, Legionnaire's disease

Table 26: Renal disease with jaundice

• Haemolytic-uraemic syndrome.
• Hepatorenal failure.
• Hepatitis B with nephrotic syndrome.
• Alcoholic cirrhosis with IgA nephropathy or renal tubular acidosis.
• Weil's disease (Leptospirosis).
• Polycystic disease with congenital hepatic fibrosis.
• Renal cell carcinoma with hepatic dysfunction e.g. cholestasis.
• Toxic – CCl_4, methoxyflurane.

Table 27: Drugs that can cause renal damage

Acute tubular necrosis
• Aminoglycosides
• Amphotericin
• Cisplatin
• NSAIDs
• Radiocontrast media
• Paracetamol poisoning
Fanconi's syndrome
• Tetracyclines (if out of date)
Glomerulonephropathy
Membranous
• Captopril (high doses)
• Gold salts
• Heavy metals
• Penicillamine
• Phenytoin
• Troxidone
Minimal change
• NSAIDs
Acute nephritis
• Penicillins
Interstitial nephritis
• Allopurinol
• Azathioprine
• Furosemide
• NSAIDs
• Penicillins
• Sulphonamides
• Thiazides
• Vancomycin
Renal tubular acidosis
Proximal
• Acetazolamide
Distal
• Amphotericin
• Lithium
Crystalluria
• Acyclovir
• Methotrexate
• Naftidrofuryl
• Sulphonamides
Renal papillary necrosis
• Aspirin plus phenacetin
• NSAIDs
Nephrogenic diabetes insipidus
• Lithium
• Dimethylchlortetracycline

- Patients with relapsing/remitting diseases (e.g. renal lupus, systemic vasculitis) must not become pregnant while taking cytotoxic agents such as cyclophosphamide. Generally, they are advised to wait until the disease has been in remission for at least 6 months.
- Patients with severe hypertension must be aware that some drugs are contraindicated in pregnancy (e.g. ACE inhibitors, ATIIR blockers) and must be discontinued in early pregnancy (by 7 weeks).
- Severely proteinuric patients are likely to become frankly nephrotic early in pregnancy, with increased risk of thrombosis.
- Patients with significant reflux nephropathy are likely to develop significant UTIs during pregnancy and should take prophylactic antibiotics throughout.
- Preconception counselling and preparation for pregnancy.

Assess renal function

- Estimate GFR
- Ultrasonography (renal size, scars, obstruction) + micturating cystography.

Assess anaemia

- Correct iron or other deficiencies
- Assess whether patient is likely to need erythropoietin therapy during pregnancy (aim to avoid transfusions).

Treat hypertension effectively

- Use 'pregnancy friendly' antihypertensives (e.g. methyldopa, labetalol, nifedipine)
- If ACE inhibition or ATIIR blockade is required for renal protection, warn patient of necessity to stop/change no later than 7 weeks (otherwise risk of ACE foetopathy).

Assess activity of renal disease or underlying systemic disease

- Urinary sediment
- SLE patients – Clinical assessment including screening for pulmonary hypertension, serology to assess disease serology.

General advice for all women contemplating pregnancy

- Stop smoking, take folic acid, reduce alcohol intake
- Advise use of contraception until patient is ready to conceive.

Management of underlying renal disease during pregnancy

- Renal function and proteinuria are measured monthly throughout pregnancy.
- Urine is screened for bacteriuria and frank infections, treated as appropriate and antibiotic prophylaxis considered.

- Patients with reflux nephropathy may need monitoring for renal obstruction with regular ultrasonography. Renal tract dilatation is normal in pregnancy and is commonly worse on the right – if there is doubt whether functional obstruction is present, it is safe to perform a DTPA scan with furosemide to assess outflow. If there is maternal kidney obstruction, the baby should be delivered. If it is not sufficiently mature, nephrostomies should be inserted to drain the kidneys.
- Hypertension is treated to maintain a BP < 140/90.
- Anaemia is monitored and treated with erythropoietin if necessary.
- Patients with anticardiolipin antibodies and those with nephrotic-range proteinuria are usually advised to undergo anticoagulant prophylaxis with low molecular weight heparin.
- If renal function deteriorates rapidly, if there is evidence of proliferative renal lesion or if hypertension or nephrotic state is severe, advice varies according to state of pregnancy. In early stages therapeutic abortion, once the foetus is viable, delivery should be expedited.
- High risk patients are given aspirin from early pregnancy to protect against pre-eclampsia.
- Pre-eclampsia is difficult to diagnose in women with significant proteinuria and hypertension. Regular foetal monitoring is essential to detect decrease in foetal growth rate and to screen for uterine artery notching. Doppler ultrasonography is a predictor of pre-eclampsia.
- The outlook for most babies of 30 weeks gestation or more is so good that it is not justified to risk the well-being of the mother by undue protraction of the pregnancy.

Renal disease caused by pregnancy. The most common cause of pregnancy-induced renal disease is ATN associated with acute volume depletion.

Causes of acute renal failure in pregnancy

Secondary to

- Hyperemesis
- Sepsis
- Hemorrhage
- Pre-eclamptic toxaemia/HELLP syndrome/acute fatty liver of pregnancy/HUS

Timing of renal impairment – The later the renal impairment occurs, it is more likely to be pregnancy-induced renal disease.

Parity of patient. Pre-eclampsia and AFLP are more common in nulliparous women, HELLP syndrome is more common in multiparous women – the group most likely to develop ARF.

Hypertension – New-onset hypertension with or without proteinuria in third trimester strongly suggests pregnancy-induced renal dysfunction.

14. URINARY CATHETERIZATION

INDICATIONS

1. Diagnosis and relief of urinary retention.
2. Management of urinary incontinence.
3. Following urological or other pelvic surgery or trauma.
4. Measurement of urine output in critically ill patients.
5. To facilitate diagnostic tests –
   a. Collection of bladder urine specimens with reduced contamination.
   b. Measurement of residual bladder urine volume.
   c. Cystometrography and cystourography

Choice of catheter – It is determined by the indication for its use.

1. *Self-retaining catheters* – A balloon or Foley catheter is preferred when the catheter must remain in the bladder – (i) A silicone coated catheter is favoured for short-term drainage. (ii) A silastic catheter is used for long-term drainage, as it is less irritant. (iii) 'Three way' Foley catheters have an extra lumen to allow continuous bladder irrigation following urological surgery or trauma (iv) Malecot's self-retaining catheter with a flower at its end which keeps the catheter in the bladder. Its use is limited to females. The flower can be collapsed during catheterization with an introducer. The catheter preferred in females is a short simple open-ended catheter.
2. *Catheters for urine sampling* – Urine samples may be obtained by catheterization in patients (usually-females) who are unable to produce adequate mid-stream urine.
3. *Suprapubic catheters* – Small suprapubic catheters are designed to pass through a hollow introducer needle, and larger ones have a trocar inside the catheter to enable insertion. A Foley catheter is cheaper and can be used.
4. *Tiemann catheter* – It is more rigid, curved tip catheter effective in negotiating the posterior urethra, particularly in males with prostaticobstruction. Disadvantage is that it is not self-retaining.
5. *Whistle-tip catheter* – is firmer and has a wide lumen and used for bladder syringing in case of clot retention.

6. *Condom catheter* – is devised by making a small nick in a condom through which a Malecot's catheter is introduced with the flower resting in the nick. Advantage is no possibility of infection since bladder is not catheterized.

Catheter size – (Size – External diameter in millimetres × 3). A small catheter 12–14F for 'in-out' and short-term catheterization. In adults who require long-term drainage, an 18–22F size is less likely to become obstructed. Length of standard Foley catheter is about 40 cm, shorter catheters are more convenient for women. Foley catheter has two balloon sizes – 5 mL and 30 mL. The larger sized balloon, which may be necessary to retain the catheter in some females and after surgery, is more likely than the smaller balloon to be associated with bladder irritation, spasm and bypassing of the catheter.

Commonly used catheters

a. Simple rubber catheter.
b. Malecot's self-retaining catheter.
c. Self-retaining Foley catheter.
d. 'Three-way' Foley catheter.
e. Short plastic open-ended catheter for use in women for obtaining urine specimen.
f. Tiemann catheter with curved end to negotiate prostatic urethra.
g. Whistle-tip catheter for syringing the bladder in clot retention.
h. Condom catheter.

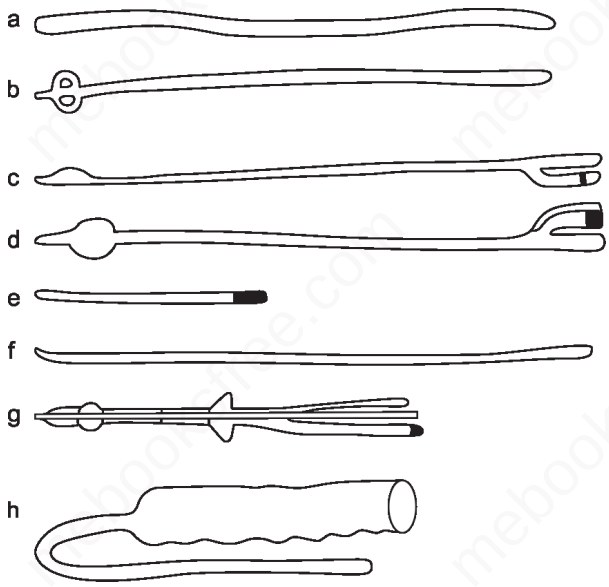


Fig. 8: Commonly used catheters

TECHNIQUE

Catheterization in men – After retracting patient's foreskin, the operator scrubs and puts on a mask, sterile gown and gloves. The glans penis and urethral meatus should be cleansed with aqueous chlorhexidine (alcoholic preparations must not be used) and sterile towels are placed around the area. Sterile 2% lignocaine jelly is then gently squeezed into the urethra. After waiting for some time to ensure adequate anaesthesia, the penis is lifted towards the patient's head and catheter inserted gently until it reaches the prostatic urethra. The penis is then lowered and the catheter pushed gently across the curve of the prostatic urethra into the bladder. A flow of urine usually indicates entry into the bladder, unless patient is anuric. If a self-retaining catheter is used, the balloon should be inflated to the volume recommended on the catheter (with sterile water or aqueous chlorhexidine). Before inflation it is necessary to ensure that the balloon is no longer within the urethra. The catheter is connected to a large volume closed drainage system, in uncircumcised patients, the foreskin must then be drawn back over the glans penis; failure to do so may cause formation of a paraphimosis.

Complications – of indwelling catheters:

1. *Bacteriuria* – Antibiotic treatment usually ineffective. Removal of catheter will be followed by disappearance of bacteriuria.
2. *Septicaemia*– is not uncommon in elderly and immunocompromised patients.
3. *Chronic bacterial prostatitis* – presents as relapsing acute cystitis in the weeks following catheter removal. It requires several weeks of treatment because of poor penetration of antibiotics into the prostate.
4. *Obstruction* – of long-term indwelling catheters by fibrous material and encrustations, hence the need for replacing the catheters at regular intervals.
5. *Urethritis* – and very occasionally, stricture formation may result from traumatic catheterization or failure to change catheters over a prolonged period.
6. *Hematuria* – from irritation of the bladder wall, usually microscopic, less commonly macroscopic.
7. *Failure of balloon deflation* – can be overcome by insertion of a ureteric catheter stylet into the balloon channel under fluoroscopic control.

15. STEM CELL THERAPY FOR KIDNEY DISEASE

Use of stem cell-based strategies have been used for treatment of situations where kidneys have been injured. They have been shown to work in acute kidney injury and repair, condition where modulating of immune response leads to healing and acts as a compliment to kidney transplantation.

1. The kidney itself is a source of variety of stem cells. Simplest example of these cells helping repair following injury is observed with acute kidney injury (AKI) due to ischaemic and toxic insult, where the renal tubular epithelial cells undergo regenerative response that leads to renal function.
2. Stem cells of bone marrow origin are responsible for the reparative process after ischaemia/reperfusion injury.
3. In clinical practice, both human embryonic (HFSCs) and allogenic/autologous haemopoietic stem cells have been used for some of the chronic kidney diseases which include autoimmune disease like SLE leading to lupus nephritis and CKD stage needing renal transplantation. Besides mesenchymal stem cells from bone marrow, umbilical cord and adipose tissue is a good source.
4. Graft versus host disease is yet another condition where immunomodularity effect of mesenchymal stem cell therapy has been used successfully when resistant to steroid therapy.

CHAPTER

9

Rheumatology

1. INVESTIGATIONS

Table 1 gives presentations of various rheumatological diseases based on presentation.

Table 1: Presentations of rheumatic diseases

Inflammatory		*Non-inflammatory*	
Monoarticular		Monoarticular	
Acute	Septic arthritis Gout Haemarthrosis Calcium pyrophosphate	Acute	Fractures Sports injuries Torn meniscus Loose body Sprain
Chronic	Tuberculosis Pauci-articular juvenile chronic arthritis	Chronic	Osteoarthritis Shoulder capsulitis Osteonecrosis Enthesitis (e.g. tennis elbow, plantar fasciitis)
Polyarticular		*Polyarticular*	
Acute	Viral Rheumatic fever Erythema nodosum	Acute	Rheumatoid arthritis Osteoarthritis (primary generalized)
Chronic	Symmetrical	Chronic	Generalized osteoarthritis Haemochromatosis Hypermobility syndrome Fibromyalgia Diabetic cheiroarthropathy
	Rheumatoid arthritis Seronegative juvenile chronic arthritis Polymyalgia rheumatic Chronic tophaceous gout		
	Asymmetrical Psoriatic arthritis		

Contd…

Inflammatory		*Non-inflammatory*	
	Inflammatory bowel disease Reiter's syndrome Pauciarticular juvenile chronic arthritis Systemic lupus erythematous Polyarteritis Systemic juvenile chronic arthritis (Still's disease)		
Spinal		*Spinal*	
Acute	Osteomyelitis Infective discitis	Acute	Disc prolapse Sprain Vertebral collapse
Chronic	Ankylosing spondylitis Spondyloarthropathies Chronic infection (e.g. brucellosis, tuberculosis)	Chronic	Spondylosis Paget's disease Neoplasia Spondylolisthesis Chronic degenerative disc disease

BLOOD TESTS

Antibodies when present are helpful in diagnosis and prognosis of autoimmune rheumatic diseases, but their absence does not exclude such diseases (Table 2).

Table 2: Autoantibodies and their relevance

Rheumatoid factor	Rheumatoid arthritis (80%), polyarteritis nodosa, cryptogenic fibrosing alveolitis
Anticyclic citrullinated peptide (Anti-CCP antibody)	Most specific marker for RA diagnosis, and also gives prognostic information
Antinuclear antibodies	Present in autoimmune diseases and other inflammatory disorders Present in 8% of the healthy population Useful screening test; other, more disease-

Contd…

Contd...

	specific antibodies are then sought IgG tends to be more pathological than IgM The higher the titre, the greater the significance
DNA	Present in 70% of patients with SLE Highly specific for SLE, but less sensitive than antinuclear antibodies Associated with lupus nephritis. Serial measures can be useful in predicting disease exacerbations in some patients
Histones	SLE (50%) Drug-induced lupus (75–90%)
U1RNP	SLE (30%), mixed connective tissue disease (also predicts Raynaud's phenomenon, deforming arthritis in these syndromes)
Sm	SLE (10-25%)
Ro and La	SLE (Ro 40%, La 15%) – associated with subacute cutaneous lupus erythematosus, photosensitive dermatitis, neonatal lupus, congenital heart block
	Sjogren's syndrome (Ro 60%, La 25%) - associated with more aggressive extraglandular systemic disease
Scl-70	Systemic sclerosis (25%) – associated with diffuse skin disease and systemic involvement, particularly cardiopulmonary
Anti RNA polymerase III	Systemic sclerosis with rapid skin involvement and contractures
Jo -1	Polymyositis (20%) – associated with interstitial lung disease
Anticentromere	Systemic sclerosis (30%)–usually limited cutaneous disease, 90% of patients with CREST
Antineutrophil cytoplasmic antibodies	cANCA – 90% of diffuse Wegener's granulomatosis, less in localized disease pANCA – broad spectrum of vasculitis and other conditions
Antiphospholipid antibodies	Includes anticardiolipin High titres of IgG antibodies plus positive lupus anticoagulant suggest greatest risk of antiphospholipid syndrome

SYNOVIAL FLUID ANALYSIS

Septic arthritis. Gram staining can give important clues to the nature of the organism and guide antibiotic treatment. Some definitive information is gained from culture of the bacteria.

Crystal disease. Uric acid crystals are needle-shaped and strongly negatively birefringent under polarized light microscopy. Between acute attacks, aspiration of an uninflamed previously affected joint can sometimes reveal uric acid crystals, and even a single crystal is pathological.

Other crystals (e.g. calcium pyrophosphate) can be identified in pseudogout.

Hemarthrosis produces uniformly blood-stained fluid that does not clot. Common causes are trauma and bleeding diathesis. Pigmented villonodular synovitis, a non-malignant neoplasm, can cause recurrent hemarthrosis in the affected joint.

BIOPSY

See Table 3 for role of biopsy in rheumatological diseases.

Table 3: Biopsies and their use in diagnosis

Skin and subcutaneous tissue
• SLE (immunofluorescence shows immunoglobulin and complement deposition at the dermo-epidermal junction) • Dermatomyositis • Scleroderma • Henoch-Schonlein purpura (IgA deposition) • Cholesterol emboli • Rheumatoid nodules (Fig.1) • Gout and other crystal tophi
Muscle
• Inflammatory myositis • Inclusion-body myositis • Metabolic and genetic myopathies • Steroid myopathy • Necrotizing vasculitis (e.g. polyarteritis nodosa) • Sarcoidosis
Salivary gland
• Sjogren's syndrome • Sarcoidosis
• **Synovium** • Chronic septic arthritis not diagnosed on synovial fluid (e.g. tuberculosis) • Crystal disease (e.g. uric acid deposits) • Pigment villonodular synovitis • Synovial chondromatosis • Sarcoidosis
Renal
• SLE with renal involvement • Wegener's granulomatosis • Henoch-Schonlein purpura (IgA deposition)
Lung
Wegener's granulomatosis- necrotizing noncaseating granuloma

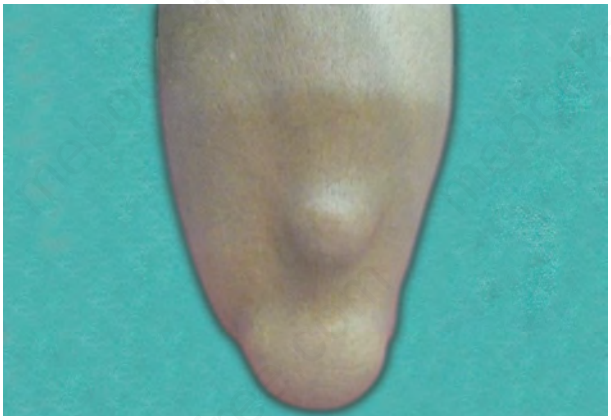


Fig. 1: Rheumatoid nodule

TESTS THAT CAN ASSIST DIAGNOSIS

ESR. It is influenced by the presence of large molecular weight plasma proteins such as fibrinogen and immunoglobulins, the concentrations of which increase in inflammation, thereby increasing the ESR. However, many other factors also affect ESR – anemia, hypercholesterolemia, greater age, female gender, obesity, pregnancy, tissue damage (e.g. stroke, myocardial infarction) and chronic renal failure increase it. Abnormal RBC shapes (e.g. sickle cell disease, microcytosis, polycythemia, CHF and cachexia decrease ESR).

C-reactive protein (CRP) is the most useful index of acute inflammation; it is specific and sensitive, increases rapidly within 6–8 hours of the initiating inflammation.

See Table 4 for the other screening tests in inflammatory arthritis.

IMAGING IN RHEUMATOLOGY

Plain radiography has limitations because changes can take months to appear in RA; only septic arthritis is likely to show abnormalities within days of onset.

Table 4: Screening tests in patients with features suggestive of inflammatory polyarthritis

Test	*Comments*
• **Urinanalysis** (microscopy)	Mandatory in all patients Renal disease not to be missed
• **Full blood count**	Leucopenia: ? SLE Thrombocytosis: ? RA Normocytic, normochromic anemia suggests aggressive disease Microcytic anemia: Possibility of haemolysis? SLE Thrombocytopenia: SLE
• **ESR and CRP**	High levels suggest aggressive disease High ESR and low CRP in some with SLE
• **Urea and electrolytes**	Kidney disease unrelated to inflammatory arthritis or part of connective tissue disease Baseline to ensure no contraindication to drugs (e.g. NSAIDs, DMARDs.)
• **Liver function tests**	Usually a baseline to ensure DMARDs are not contraindicated
• **Thyroid function tests**	Hypothyroidism causes polyarthralgia, is more common in inflammatory arthritis, is not always obvious and is easily treated
• **Bone biochemistry**	Can sometimes suggest suspected malignancy that can present with polyarthralgia/polyarthritis
• **Glucose**	Baseline if corticosteroids might be needed
• **Rheumatoid factor**	May help diagnosis and prognosis. Repeated testing unnecessary
• **Antinuclear antibodies**	May help diagnosis and prognosis, particularly if specificities are positive
• **Other tests** (depending on clinical situation)	Occasionally immunoglobulins, complement levels and breakdown products, muscle enzymes (if myositis also suspected)

Contrast arthrography is performed by injecting contrast medium or air into a joint before radiography or CT. It is particularly helpful in the knee and shoulder to identify meniscal tears, intra-articular loose bodies and transchondral fractures.

Ultrasonography is used to identify a Baker's cyst of the knee, but also provides an assessment of joint effusion, synovial proliferation, intra-articular loose bodies and tendon thickening.

Isotope scanning using technetium is used to seek bone metastases. It also demonstrates bone or joint infection and inflammation, because it shows increased blood flow to, or increased metabolic activity in bone, joints or entheses. This modality is perhaps most useful in excluding significant inflammatory, infective or neoplastic musculoskeletal disease.

CT demonstrates bone well and can be used for peripheral joints and spine. Three-dimensional reconstruction of images can be useful in the spine (e.g. to diagnose spinal stenosis).

MRI is superior to CT in imaging soft tissues and is particularly helpful in the diagnosis of musculoskeletal disorders. It is the best method for demonstration of intervertebral disc pathology and prolapse, and pressure on spinal nerve roots form disc herniation, rheumatoid subluxation or spinal stenosis. It has revolutionized detection of soft tissue lesions in knee and shoulder. It can be used to assess muscle involvement in polymyositis.

GENES AND ENVIRONMENT IN RHEUMATIC DISEASES

Single-gene disorders – A single-gene disorder is one in which all the features of the disease can be attributed to one family gene (e.g. the *HFE* gene in hemochromatosis). The faulty gene contains nucleotide changes that have consequences for the translated protein. The genetic abnormalities can lead to the same clinical phenotype because they all result in the lack of an essential protein (Table 5).

Polygenic disorders – A polygenic disorder is one in which family or twin studies show evidence of heritability but a Mendelian pattern of inheritance is not seen. For example, nodal generalized osteoarthritis commonly runs in families and shows a strong female predominance but is not inherited predictably.

Comparison of the concordance of disease in monozygotic twins (genetically identical), and dizygotic twins (average 50% of genes in common) gives an indication of the role of genetic influences, e.g. in ankylosing spondylitis,

Table 5: Monogenetic disorders with rheumatic consequences

Disease	*Rheumatic Phenotype*	*Genes involved*
Familial chondrocalcinosis	Pseudogout	ANK – a gene controlling extracellular and intracellular pyrophosphate levels
Familial expansile osteolysis	Paget's disease-like lesions	RANK
Blau's syndrome – familial	Granulomatous synovitis	*CARD15/NOD2* - also associated with Crohn's disease arthritis, iritis and rash
Disease	*Rheumatic Phenotype*	*Genes involved*
Multiple epiphyseal dysplasia	Growth abnormalities	Cartilage oligomeric protein, type IX collagen, matrilin-3
Multicentric osteolysis and arthritis syndrome	Vanishing bone syndrome	Matrix metalloproteinase 2
Familial Mediterranean syndrome	Recurrent serositis	Marenostrin
TRAPS	Periodic syndrome	Tumor necrosis factor α-receptor 1

50–70% of monozygotic twins are disease concordant, compared with about 25% of dizygotic twins.

Environmental influences on genes – The HLA genes particularly HLA-B27 in spondyloarthropathies and HLA-DR4 (with related alleles) in RA, are excellent examples of gene-environment interactions, because HLA antigens are the principal means by which the adaptive immune system recognizes the environment-HLA antigens present peptides derived from pathogens and self-proteins to T cells.

2. RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a multisystem inflammatory disease primarily affecting the synovium and adjacent tissues.

AETIOLOGY

Immunogenic factors (e.g. HLA-DRB1) are important in determining the development and expression of the disease. The combination of conserved amino acid sequence in the third hypervariable region of HLA-DRB1 with positive rheumatoid factor identifies individuals at 13 times greater risk of developing bony erosions at 1 year.

Other factors – (a) Hormonal factors – Incidence of RA in women is greater before menopause and remission of RA during pregnancy is well known. (b) Oral contraceptive pill – has no effect on RA risk overall, however it may postpone onset of the disease. (c) Low economic status is associated with a worse disease outcome in RA.

PATHOGENESIS

Once the inciting agent has activated the immune system, a range of intersecting immunological pathways operate, leading eventually to joint destruction. Joint deformity occurs in RA because the cartilage and then the bone is eroded by the proliferative synovial tissue. This process leads to increased laxity of ligaments around the joints, subluxation of tendons and subsequently of joints, and inflammation of many other tissues in the body.

Table 6 gives American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis.

PRESENTATION

RA presents as acute polyarthritis developing over a few days, or more commonly, weeks to months. The initial pattern of joint involvement may be monoarticular, oligoarticular (≤4 joints) or polyarticular (>5 joints), usually in a symmetric distribution. Systemic features such as fatigue and diffuse musculoskeletal pain may occur before frank swelling of joints. The disease commonly presents in the metacarpophalangeal joints or metatarsophalangeal joints and wrists (Fig. 2). Morning stiffness is a common

Table 6: ACR classification criteria for rheumatoid arthritis

		Score
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative anti-CCP	0
	Low-positive RF or low-positive anti-CCP antibodies (<3 times ULN)	2
	High-positive RF or low-positive anti-CCP antibodies (>3 times ULN)	3
Acute phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP and abnormal ESR	1
Duration of symptoms	<6 weeks	0
	>6 weeks	1
Score > 6 indicates definite RA		

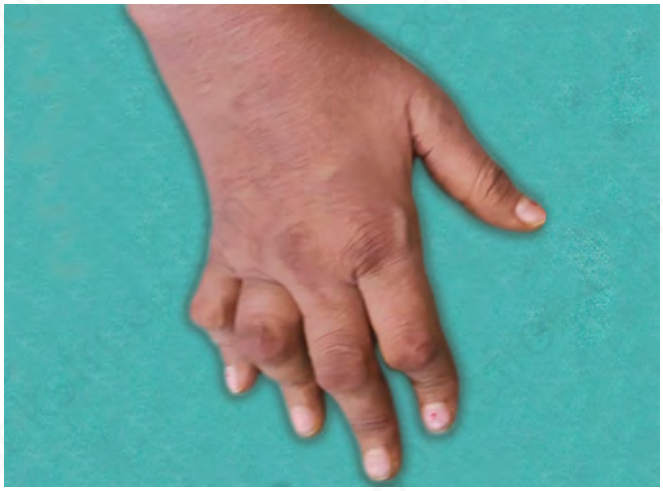


Fig. 2: Rheumatoid hand

early feature and boggy synovial tissue can be demonstrated on examination.

COURSE OF THE DISEASE

Clinically RA behaves in various ways, however most patients who have RA for more than 6 months develop progressive, erosive disease leading to significant disability. Up to 10% develop acute and progressive disease and up to 20% experience a single episode of inflammatory polyarthritis and do not suffer further.

RA causes significant morbidity – 50% of individuals with RA are unable to work 10 years after its onset, and life expectancy is reduced by 5 years in women and 7 years in men. Excess mortality is usually from cardiovascular disease.

Few patients enter true remission. ACR criteria for remission are given in Table 7.

Exclusions: Clinical manifestations of acute vasculitis, pericarditis, pleuritis or myositis and/or unexplained recent weight. loss or fever secondary to RA do not allow a definition of complete remission.

Table 7: ACR/EULAR provisional definition of remission in rheumatoid arthritis

At any time point, patient must satisfy all of the following:
• Tender joint count ≤1
• Swollen joint count ≤1
• C-reactive protein ≤1 mg/dL
• Patient global assessment ≤1 (on a 0–10 scale)

OR

At any time point, patient must have a Simplified Disease Activity Index score of ≤3.3

Table 8: Features associated with a poor prognosis in rheumatoid arthritis

• Greater number of joints affected
• Uncontrolled polyarthritis
• Structural damage/deformity (e.g. erosions on joint radiographs)
• Functional disability
• Presence of extra-articular features (nodules, vasculitis)
• Psychosocial problems (e.g. poverty, low educational achievement, employment requiring moderate/heavy labour)
• High titre of rheumatoid factor
• Presence of HLA-DR4, particularly homozygosity
• Family history

See Table 8 for the features associated with poor prognosis in rheumatoid arthritis.

Types of Presentation

1. *Classical* – Pain, stiffness and swelling of small joints of hands and wrists. Symptoms fluctuate in severity from day to day.
2. *Palindromic* – Intermittent episodes of pain, swelling and redness, usually of a single joint, followed by rapid return to normal after several days.
3. *Systemic* – Weight loss, pleurisy and pericarditis but minimal joint involvement.
4. *Polymyalgic* – Pain and stiffness in shoulders and hips with subsequent synovitis.
5. *Monoarthritic* – Single joint involvement, usually the knee.
6. *Acute onset* – Sudden overnight onset with stiffness and pain.
7. *With generalized lymphadenopathy.*

DIAGNOSIS

a. The *clinical criteria* for the disease must have been present for at least 6 weeks. The joints feel hot and swollen and are usually tender to touch, and generalized lymphadenopathy may also be present.

b. *Laboratory:* Abnormal investigations may include:
   - Increased WBC count
   - Thrombocytosis
   - Mild normocytic anemia
   - High ESR or acute phase reaction
   - Positive rheumatoid factor
   - Positive anti-CCP antibody
   - Arthrocentesis of synovial fluid shows it to be straw colored with increased neutrophils

DIFFERENTIAL DIAGNOSIS

Other disorders presenting with pain and tenderness:

- Infectious arthritis – Viral (rubella, rhinovirus type 7, echovirus, E-B virus, hepatitis C), bacterial (*Mycoplasma*, Lyme disease)
- B27-associated arthropathies, which usually present as oligoarthropathy (psoriatic, reactive and enteropathic)
- Crystal arthropathies – Gout and calcium pyrophosphate dihydrate deposition disease

JOINT INVOLVEMENT IN RA

Joints commonly involved are metacarpophalangeal, proximal interphalangeal joints, the wrists and the knees. In early stages joints are warm, swollen and tender. Weakening of the joint capsule and tendon along with ligament damage lead to joint instability, subluxation or dislocation and so produces characteristic deformities of RA. Eventually severe joint damage may lead to fibrous or bony ankylosis or secondary degenerative changes. Some of the characteristic joint features of RA are listed in Table 9.

Temporomandibular joints – may be affected in up to 30% of patients, most commonly young women.

Cricoarytenoid joints – may occasionally be affected causing dysphagia, hoarseness or stridor.

Extra-articular features of RA – Systemic features in RA may dominate articular manifestations and in some individuals may predate joint disease. Systemic manifestations may be divided into organ-specific and general.

SPECIFIC ORGAN INVOLVEMENT IN RA

Cutaneous – Livedo reticularis, palmar erythema, pyoderma gangrenosum (very rare).

Subcutaneous nodules – occur in 20–30% of cases. Vary between 3 and 20 mm in diameter, single or multiple, occurring over bony prominences, at sites of pressure or friction, e.g. elbow. Can breakdown and become infected. Their presence indicates an adverse prognosis Tenosynovitis. May also occur in the lungs, pleura, pericardium and peritoneum.

Myositis – Muscle wasting around inflamed joints, e.g. guttering between extensor tendons and dorsal surface of the hand, and wasting of quadriceps.

Bone – Generalized osteoporosis especially of vertebral bodies. Spontaneous vertebral collapse and wedging may occur.

Vascular – Vasculitis: (a) Small nail-fold and nail-edge infarcts, or sometimes gangrene of the digits. (b) Purpuric rashes caused by capillaritis. (c) Indolent leg ulcers due to small vessel vasculitis. (d) Arrhythmias and heart block rarely from formation of small nodules in conducting system. (e) Rarely myocardial infarction secondary to vasculitis. (f) Neurovascular disease presenting as distal sensory neuropathy or mononeuritis multiplex.

Hematological – (1) Anemia – Pathogenesis – (a) Active inflammatory disease. (b) Felty's syndrome. (c) Iatrogenic – Aspirin/NSAID-induced GI bleeding. (i) Gold, penicil-

Table 9: Joint deformities in rheumatoid arthritis

Joint	*Main deformities*	*Main problems*	*Principal solutions for medical failure*
Fingers	• Boutonniere • Swan-neck • Ulnar deviation • Mallet	• Functional (especially swan-neck) • Cosmetic	• Splinting • Surgery
Wrists	• Subluxation	• Functional • Carpal tunnel syndrome • Pain	• Splinting • Arthrodesis
Elbows	• Fixed flexion	• Pain • Functional	• Synovectomy • Arthroplasty • Other surgery
Shoulders	• Superior subluxation	• Functional (global loss of movement) • Pain	• Arthroplasty • Suprascapular nerve block
Neck	• Atlantoaxial subluxation • Subaxial stepwise deformity	• Cervical myelopathy • Pain	• Hard collar • Surgical fixation
Knees	• Valgus deformity	• Pain • Instability	• Synovectomy • Arthroplasty • External brace
Ankles and subtalar joint	• Valgus deformity	• Pain • Instability	• Supportive footwear • Surgery
Joint	*Main deformities*	*Main problems*	*Principal solutions for medical failure*
Midfoot	• Pes planus	• Pain	• Valgus insoles, supportive footwear, surgery
Toes	• Valgus	• Pain	• Accommodating footwear
	• Cock-up	• Bursitis and ulcers	• Chiropody • Supportive insoles • Surgery
Hips	• Fixed flexion	• Pain • Global loss of function	• Arthroplasty

lamine-induced hypoplastic anemia. (ii) Sulfasalazine-induced hemolysis. (2) Lymphadenopathy.

Cardiac – (a) Mitral regurgitation. (b) Pericardial effusion. (c) Constrictive pericarditis. Have increased risk of coronary artery disease.

Respiratory system – (a) *Pleurisy and pleural effusions*. (b) *Rheumatoid nodules* – may be parenchymal or subpleural, solitary or multiple. (i) May cavitate and cause hemoptysis. (ii) In rheumatoid patients exposed to certain dusts, e.g. coal miners, nodules are accompanied by massive fibrotic reactions (Caplan's syndrome). (c) Fibrosing alveolitis – starts in lower lobes and gradually spreads upwards. (d) Obliterative bronchiolitis – rare complication, may be associated with penicillamine therapy. (e) Pulmonary hypertension. (f) Bronchopleural fistulae. (g) Stridor due to – (i) Cricoarytenoid arthritis. (ii) Nodule on vocal cords. (h) Recurrent lower respiratory tract infection (Sjogren's). (i) Iatrogenic – (i) Asthma (salicylates). (ii) Allergic/fibrosing alveolitis (gold). (iii) Goodpasture's (penicillamine). (iv) Interstitial fibrosis (methotrexate, chlorambucil).

Neurological – (a) *Neuropathy* – (i) Entrapment neuropathies – most often median nerve compression producing carpal tunnel syndrome. (ii) Peripheral neuropathy – usually sensory, occasionally sensorimotor. (iii) Vasculitis may rarely affect large nerves producing mononeuritis multiplex. (b) *Cervical cord compression* – caused by cervical subluxation may cause sudden death, or more commonly progressive cervical myelopathy. (c) *Cervical nerve root compression* – Pain, numbness or paraesthesia in arm or hand. (d) *Muscle wasting* – (a) Mechanisms – (i) Systemic hypermetabolism. (b) Disuse atrophy. (c) Inflammatory (vasculitic) myositis. (d) Neuropathic – (i) Vasculitic. (ii) Entrapment. (iii) Splint-induced nerve compression. (d) *Iatrogenic* – Corticosteroid myopathy.

Renal – No specific kidney lesion. Proteinuria, sterile pyuria, microscopic hematuria, casts and reduced glomerular function often occur. Analgesic nephropathy, drug-induced interstitial nephritis or chronic pyelonephritis may be seen in some cases. Secondary amyloidosis is rare but important cause of kidney disease.

Ocular – (a) Keratoconjunctivitis sicca. (b) Episcleritis and scleritis.

Reticuloendothelial system – (a) *Splenomegaly* – in about 5%. Mechanisms – (i) Primary disease manifestation. (ii) Felty's syndrome. (iii) Sjogren's syndrome. (iv) Amyloidosis. (b) *Generalized lymphadenopathy* – in about 50% of patients with active RA. (c) *Oedema* – of feet and ankles due to poor lymphatic drainage. RA patients have increased risk of lymphoma specially in cases of uncontrolled disease activity and Felty's syndrome.

Infection – Increased frequency in RA. – (a) *Antinuclear antibodies* – in 50%. (b) *Other abnormalities* – which reflect acute phase response – Elevated CRP, alkaline phosphatase and platelets. Decreased serum albumin and hemoglobin.

Amyloidosis – usually manifested by proteinuria. Malabsorption if GI tract involvement.

Non-specific features seen in most patients with active RA include lethargy, depression and malaise. Fever is occasionally an early feature, particularly in systemic disease. Weight loss may be a marked feature. Risk of malignancy is increased in RA; this relates principally to hematological disorders. Incidence of some solid organ tumors (e.g. adenocarcinoma of the lung) is also increased. Reduced bone density can lead to an increased risk of fractures. Amyloidosis may contribute to kidney or hepatic failure in some patients.

ORGAN SPECIFIC AND SYSTEM-SPECIFIC FEATURES

Sjogren's syndrome – is the most common syndrome which occurs in up to 40% of patients with RA. There is dryness in eyes, nose and mouth as a result of generalized exocrinopathy. Lethargy appears more intense in these patients and there is an association later with lymphoma, though this risk is less than that in patients with primary Sjogren's syndrome.

Felty's syndrome is much less common. It is characterised by severe RA, splenomegaly and neutropenia. There is greater risk of systemic infection and development of chronic leg ulcers.

INVESTIGATIONS

1. ***Tests for inflammation*** – Raised ESR, C-reactive protein and plasma viscosity. Other laboratory tests to support inflammatory disease – Normochromic, normocytic anemia (with low iron levels and iron-binding capacity), thrombocytosis, elevated hepatic alkaline phosphatase, polyclonal gammopathy, and elevation of acute phase proteins, e.g. ferritin.
2. ***Immunological tests*** – (a) *Rheumatoid factor* – RF is an autoantibody directed against the Fc fragment of immunoglobulin G (IgG). The commonly used Rose-Waller Latex agglutination tests detect only the IgM type of RF, because IgM is a multivalent immunoglobulin and hence a better agglutinator. Rose Waller test is expressed as differential agglutination titre (DTA); DTA above 1 in 16 is significant. See Table 10 for conations associated with presence of rheumatoid factor.

Table 10: Conditions in which RF may be present

- *Rheumatoid arthritis*
- *Connective tissue disease* – SLE, Sjogren's syndrome, systemic sclerosis, mixed connective tissue disease.
- *Other diseases with immunological factors* – Chronic active hepatitis, sarcoidosis, fibrosing alveolitis, Paraproteinaemias, cryoproteinaemias.
- *Chronic infections* – Infective arthritis, pulmonary tuberculosis, leprosy, syphilis, infectious mononucleosis, leishmaniasis.
- *Miscellaneous* – Normal individuals especially aged, relatives of patients with RA, myeloma.
- *Mixed essential cryoglobulinaemia.*
- *Anti-nuclear antibodies* – Test may be positive, particularly in patients with extra-articular disease manifestations.

(b) Anti-CCP predates diagnosis of RA and may be found years before symptoms of RA develop, especially in older individuals. High levels of the antibody indicate a more aggressive form of RA.

3. ***Radiology*** – *Sequence of changes* – (a) Periarticular osteopenia with soft tissue swelling. (b) Erosions at joint margins (Fig. 3) at junction of synovium, subchondral bone and articular cartilage. (c) Loss of joint space. (d) Deformity such as subluxation or complete dislocation of affected joints (Fig. 4).
4. ***Special investigations*** –
   a. *Synovial biopsy* – Rheumatoid pattern (villus formation with thickening of synovial layer and infiltration with abnormal cells) in rheumatoid arthritis (also in Still's disease, SLE).
   b. *Synovial fluid* – Not helpful in differential diagnosis from other types of inflammatory arthritis. WBC counts between 5000 and 50000 WBC/μL compared to <2000 WBC/μL for a non-inflammatory condition such as osteoarthritis. Overwhelming cell type in the synovial fluid is the neutrophil.
   c. *Arthroscopy* – will not distinguish RA from various inflammatory seronegative arthritides. In acute RA synovium is oedematous, diffusely erythematous and friable. In more chronic conditions, it becomes thickened, polypoid.
   d. *Renal biopsy* – if reduced glomerular or tubular function.
   e. *Pulmonary biopsy* – to distinguish rheumatic nodules from carcinoma or to establish diagnosis of fibrosing alveolitis.

MANAGEMENT OF RHEUMATOID ARTHRITIS

General Measures

Education – Provides information on the disease and its therapies. It also emphasizes the role of patients in caring for and controlling their own disease.

Exercise – Much of the pain and stiffness in RA arises from periarticular tissues such as muscles and tendons and patients should perform a general (range of motion) exercise programme, to improve and maintain muscle bulk around the joints.

Physiotherapy/occupational therapy – Physiotherapeutic modalities such as electric therapy (ultrasound or interferential), heat or cold. Joint protection in form of splinting to prevent deformity during episodes of acute pain and advice regarding transference of load or alternative ways of performing tasks have an important role.

Dietary advice includes weight reduction and the addition of fish oil or evening primrose oil. Fish oil substitutes

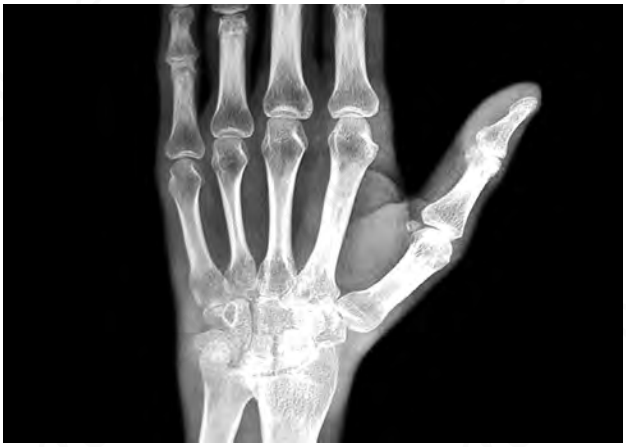


Fig. 3: X-ray hand in early rheumatoid arthritis

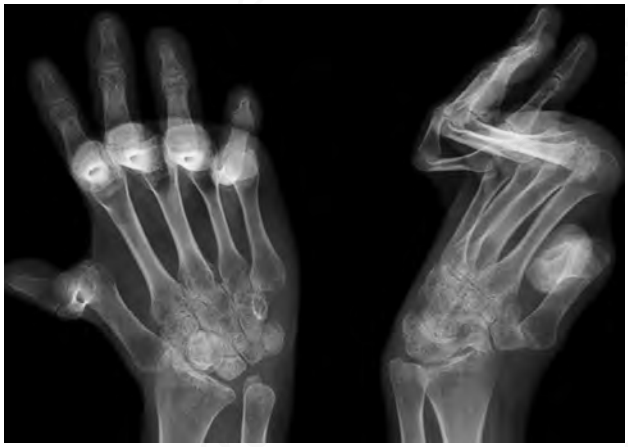


Fig. 4: X-ray hand showing subluxation of wrist and MCP joints

have enabled reduction or discontinuation of NSAIDs in some patients with RA.

Pharmacotherapy

Once the diagnosis of RA has been confirmed, treatment with drugs that retard joint destruction and reduce disability (disease-modifying antirheumatic drugs) should be commenced promptly. NSAIDs have no effect on long-term disability but provide symptom relief. Pure analgesic agents such as paracetamol can provide pain relief and reduce dose requirements of:

NSAIDs

NSAIDs are derived from various chemical classes with a common mechanism of action – reduction of prostaglandin synthesis (Table 11). The response to NSAIDs varies and it is important to find the right NSAID for each patient.

Risk Factors for Gastric Toxicity of NSAIDs

Definite

- Age > 65 years
- Smoking
- Prior ulcer disease or complications
- High-dose multiple NSAIDs
- Concomitant corticosteroid therapy

Possible

- Alcohol
- Presence of *H. pylori*

Table 11: Non-steroidal anti-inflammatory drugs (NSAIDs)

Drug	*Dose*	*Potential adverse effects*
Propionic acids		**Gastrointestina (common)**
• Ibuprofen	• 400–800 mg qds	• Indigestion, unceration, hemorrhage, perforation
• Benoxaprofen	• 600 mg o.d.	• Small bowe uceration
• Fenoprofen	• 600 mg o.d.	• Stomatitis
• Ketoprofen	• 100 mg t.d.s	**Renal (common)**
• Naproxen	• 500 mg b.d.	• Increased serum creatinine level
• Zaltoprofen	• 80 mg b.d	• Renal faiure
Fenamic acids		• Oedema, worsening of heart failure
• Flufenamic acid	• 200 mg qds	• Interstitial nephritis
• Mefenamic acid	• 500 mg qds	• Papillary necrosis
• Tenidap	• 120 mg qds.	**Cardiac (reatively common)**
Oxicams		• Fluid retention
• Piroxicam	• 20 mg o.d.	• Cardiac flaiure
• Tenoxicam	• 20 mg o.d.	• Hypertension
• Meloxicam	• 15 mg o.d.	**Neurological (uncommon)**
Phenylacetic acids	• 50 mg b.d. or	• Headache
• Diclofenac	• 100 mg slow release o.d.	• Dizziness
• Fenclofenac	• 600 mg b.d.	**Pulmonary (rare)**
• Aceclofenac	• 100 mg b.d.	• Exacerbation of asthma
Indole derivatives	• 25 mg t.d.s. or	**Dermatological (rare)**
• Indomethacin	• 75 mg nocte or suppository	• Erythema nodosum or variants (Stevens-Johnson syndrome and toxic epiderma necrolysis)
• Sulindac	• 100 mg nocte	• Bullous eruptions
• Tolmetin	• 200 mg b.d.	• Fixed drug eruption
	• 400 mg qds	• Urticaria
Pyrazolones		**Hematological (rare)**
• Oxyphenbutazone	• 100 mg t.d.s	• Aplastic anemia
• Azapropazone	• 600 mg b.d.	• Hemolytic anemia (mefenamic acid ony)
• Febrazone	• 200 mg t.d.s.	**Hepatic (rare)**
Naphthylalkanones		• Hepatitis
• Nabumatone	• 1 g daily	**Systemic (rare)**
COX-2 inhibitors		• Anaphylactoid reactions
• Valdecoxib	• 20–40 mg b.d.	• Comparativey ess
• Celecoxib	• 200 mg b.d.	• GI upset
• Etoricoxib	• 60–120 mg o.d.	• GI side effects
• Etodolac	• 300 mg b.d.	

DMARDS

The onset of effect is usually delayed (4 weeks to 3 months) and they have various mechanisms of action. They can alter laboratory markers of inflammation such as CRP and ESR. Incidence of toxicity is similar to NSAIDs.

Biologics

Such as IL-1 receptor antagonists and anti TNF-α agents exert their anti-inflammatory action by neutralizing the activities of TNF-α and IL-1 respectively. In contrast to older DMARDs, these agents have rapid onset of action with fewer side effects and have pronounced disease reducing activity in patients who have been treated with other DMARDs, when administered as monotherapy or in combination with methotrexate in patients with active RA.

Guidelines for anti-TNF-α therapy (British Society for Rheumatology)

- Active disease: Disease activity score (DAS) > 5.1
- Pretreatment: Failure of at least two DMARDs after adequate trial
- Exclusion: Pregnancy or breast feeding
  Active infection
  High risk of infections
  Malignancy or premalignancy

Table 12 gives drugs and their dosages and toxicities used in rheumatoid arthritis.

Table 12: Drugs used in rheumatoid arthritis.

Drug	*Dose regimen*	*Adverse effects / Monitoring*
1. DMARDs		
Hydroxychloroquine	200 mg b.d. till response, then 200 mg o.d.	Retinal maculopathy. Ophthalmoscopy before treatment and at 6 and 12 months.
D-penicillamine	125 mg at night, increased by 125 mg/month. Maximum 1000 mg.	Maculopapular rash. Anorexia, nausea, loss of taste, mouth ulcers. Proteinuria. Thrombocytopenia, pancytopenia. Drug-induced SLE. Myasthenia gravis. Pemphigus reaction. Goodpasture's syndrome. Full blood count, urinalysis fortnightly until dose stable, then monthly.
Gold compounds		
Intra-muscular	Test dose 10 mg, then 20–50 mg/week. Once remission, 50 mg/month.	Rash. Stomatitis. Proteinuria. Thrombocytopenia, pancytopenia. Full blood count. Urinalysis before each injection.
Oral	3 mg b.d.	Less toxic than i.m. gold but similar hematological and renal problems can occur. Full blood count and urinalysis monthly.
Methotrexate	7.5 mg one weekly, increased in 2.5 mg increments to 15–20 mg	Marrow suppression, liver damage. Teratogenicity. Early introduction of MTX therapy in undifferentiated arthritic (UA) pts. Seropositive for anti-CCP delays differentiation of RA and retards the progression of joint destruction.
2. Corticosteroids		
Prednisolone	7.5 mg/d, monthly pulses with high dose when DMARD started Intra-articular injections into inflamed joints. IM or IV during flare up	Useful additive to control symptoms Adverse effects of steroids
3. Biologic response modifiers		
TNF-α antagonists		
Etanercept	25 mg/s.c. twice a week	Inj. site reaction, URI development of ANA and antibodies to the drug
Infliximab	5 mg IV at 0.2–6 week and every 8 weeks thereafter	+/- SR, hypotension headache rash, autoantibodies
Adalimumab	40 mg s.c. every 2 weeks	ISR, URI, rash, headache, sinusitis
Golimumab	50 mg s.c. monthly	ISR
Certolizumab	400 mg s.c weeks 0, 2, 4, then 200 mg every other week	ISR

Contd…

Contd…

Drug	*Dose regimen*	*Adverse effects / Monitoring*
T-cell inhibitor		
Abatacept	Weight based <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1000 mg IV dose at weeks 0, 2 and 4 and then every 4 weeks OR 125 mg s.c weekly	↑ Risk of bacterial, viral infections
Anti CD-20 antibody		
Rituximab	1000 mg IV x 2, days 0 and 14 May repeat course every 24 weeks or more	↑ Risk bacterial, viral infections, infusion reaction, Hepatitis B reactivation, cytopenias
Anti-IL-6 receptor antibody		
Tocilizumab	4–8 mg/kg IV monthly Or 162 mg s.c. every other week (<100 kg weight) 162 mg s.c. every week (≥100 kg weight)	Risk of infection, Infusion reaction LFT elevation, Dyslipidemia, Cytopenia
IL-2 receptor antagonist		
Anakinra	100 mg s.c./day	ISR, infections, neutropenia
4. JAK pathway inhibitor		
Tofacitinib	5 mg orally bd	Risk of infection, LFT elevation, Dyslipidemia Neutropenia
5. Immunosuppressants		
Azathioprine	25 mg/kg/day	Marrow suppression. Occasional liver damage. Carcinogenesis. Full blood count, LFTs 2 weekly for 2 months, then monthly. Regular urinalysis.
Leflunomide	100 mg o.d. for 3 days, then 20 mg o.d.	Hepatotoxicity, diarrhea, hair loss, rash
Cyclosporine	3–5 mg/kg/day	Nephrotoxic, Hypertension, Hyperkalaemia
Cyclophosphamide	2–3 mg/kg/d	Bone marrow suppression, may be lifesaving in serious organ involvement

Side effects – Long-term therapy can cause weight gain, bruising, fluid retention, susceptibility to infection, diabetes, osteoporosis. With corticosteroid therapy, the following should be noted:

- Anti-osteoporotic drugs (calcium, 1.25-dihydrocholecalciferol or bisphosphonates) in all patients on long-term (>3 months) therapy.
- Use lowest possible dose (< 7.5 mg daily) as morning dose.
- Plan a slow dose reduction (1 mg every month) in patients in whom the disease is relatively quiescent or the side effects are becoming a problem.

Special Indications for Steroids

(first line agents) in RA

1. Pregnant women with RA
2. Rheumatoid vasculitis (high dose with cyclophosphamide)
3. Ocular disease
4. Elderly patients and those with mild to moderate renal insufficiency (low dose).

Other Treatments

a. The concept that RA behaves much like a slowly invasive tumor moving across the joint causing cartilage destruction has led to the use of high dose chemotherapy with stem cell rescue. Genetic therapies approaches with the aim of increasing local expression of anti-inflammatory molecules in the involved synovial tissues are likely to provide significant benefits in patients with RA.

b. Stem cell transplantation of donated hematopoietic stem cells, which mature into various blood cells have induced remission in some children with severe juvenile RA.

c. Plasmapheresis. A device called prosorba column is used to remove inflammatory antibodies from the patient's blood. This therapy may slow or even halt progression of the disease in a good number of patients.

Surgery

In patients with significant joint destruction, surgical techniques such as arthroplasty and/or excision (as in forefoot reconstruction or wrist arthrodesis) can provide pain relief and improve function.

3. SPONDYLOARTHROPATHIES

SPONDYLOARTHROPATHIES

Is a group of disorders characterized by:

- Involvement of sacroiliac joints
- Peripheral arthropathy
- Absence of rheumatoid factor
- Pathological changes at sites of insertion of ligaments or tendons (enthesopathy)
- Involvement of lungs, heart, skin and eye (iritis)
- Clinical evidence of overlap between members of the group
- Tendency towards familial aggregation – association with HLA-B27 ranges from about 60% in psoriatic and enteropathic spondylitis to more than 90% in ankylosing spondylitis depending on ethnic group.

ANKYLOSING SPONDYLITIS

Is symptomatic sacroiliitis (persistent pain and stiffness for >3 months associated with morning stiffness and improvement with exercise/worsening with rest). Various diagnostic criteria of spondyloarthropathy are given in Tables 13 and 14.

New criteria introduced by Assessment of Spondyloarthritis International Society (ASAS) is given in Table 15.

Table 13: New York criteria for diagnosis

Clinical criteria
• Limited movement of lumbar spine in three planes
• Pain in lumbar spine or at lumbodorsal junction
• Chest expansion < 2.5 cm
Radiological
Unilateral sacroiliitis grade III–IV, or bilateral sacroiliitis grade II

Table 14: European spondyloarthropathy group criteria

Inflammatory spinal pain of synovitis (asymmetrical or predominantly in lower limb) and one or more of the following:
• Positive family history
• Psoriasis
• Inflammatory bowel disease
• Buttock pain
• Enthesopathy
• Sacroiliitis

Table 15: ASAS criteria for classification of axial spondyloarthritis

(To be applied for patients with back pain ≥3 months and age of onset < 45 years) A. Sacroiliitis on Imaging Plus ≥1 SpA Feature • Sacroiliitis on imaging – Active (acute) inflammation on MRI highly suggestive of SpA associated sacroiliitis and/or – Definite radiographic sacroiliitis according to modified New York criteria (as mentioned in Table 13)
OR
B. HLA-B27 Plus ≥ 2 Other SpA Features SpA features considered for diagnosis are as follows: • Inflammatory back pain • Arthritis • Enthesitis (heel) • Anterior uveitis • Dactylitis • Psoriasis • Crohn's disease or ulcerative colitis • Good response to NSAIDs • Family history of SpA • HLA-β27 • Elevated CRP

Aetiology

(a) *Sex* – More common in men than in women (2.7:1). Women tend to have more peripheral joint involvement, men have more spinal disease. Women are more likely to suffer inflammatory bowel disease (particularly Crohn's) as a co-morbidity, men more psoriatic spondylitis. (b) *Genetic factors* – HLA-B27 and HLA-DR1 confer susceptibility to the spondyloarthropathies. However, the entire HLA locus accounts for no more than 50% of the genetic susceptibility and loci on other chromosomes (e.g. 1, 2, 9, 10, 16) confer additional susceptibility, with severity loci on chromosomes 18, 19 and 21. (c) *Environmental triggers* of the disease remain unknown. Gram-negative organisms such as *Salmonella, Sh. flexneri, Campylobacter* and *Yersinia* precipitate reactive arthropathy.

Clinical Features

Suggestive of ankylosing spondylitis

- Insidious onset of discomfort
- Age at onset <40 years
- Persistence of symptoms for >3 months
- Association with morning stiffness
- Improvement with exercise

Ankylosing spondylitis does not burn out, it continues to be active. Fatigue is a major component. No system in the body is unaffected.

Sacroiliac joints and spine – Early sign is evidence of sacroiliac joint arthritis (Figs. 5 to 7). Examination of spine

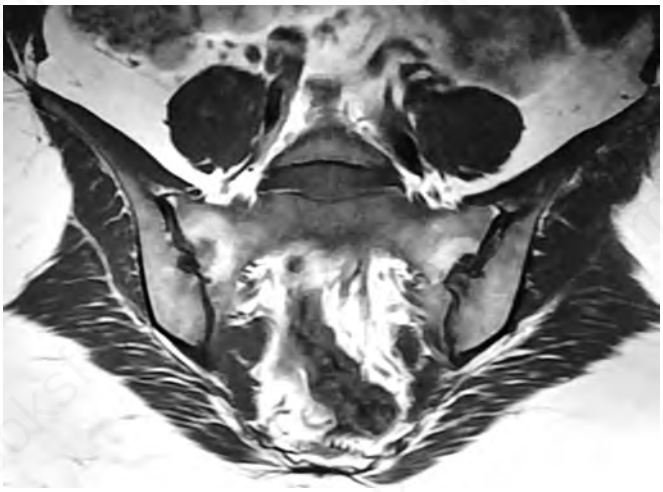


Fig. 5: MRI sacroiliac joint showing erosions and subchondral oedema

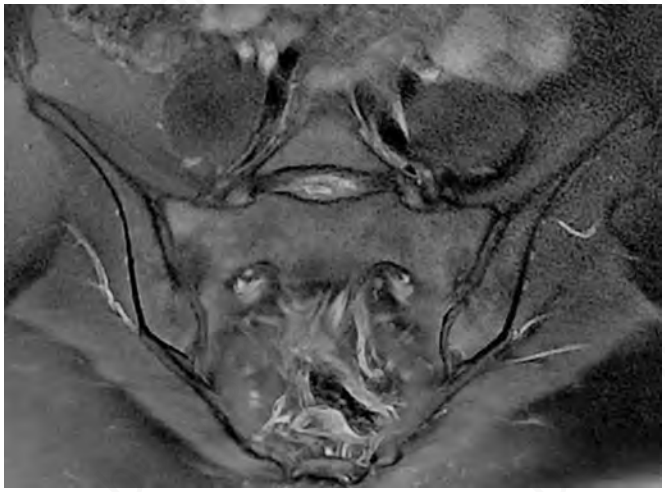


Fig. 6: MRI sacroiliac showing erosions

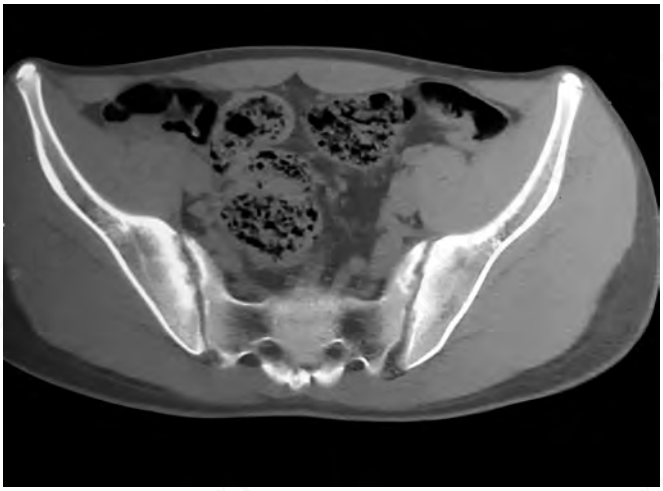


Fig. 7: CT SI joints showing erosions

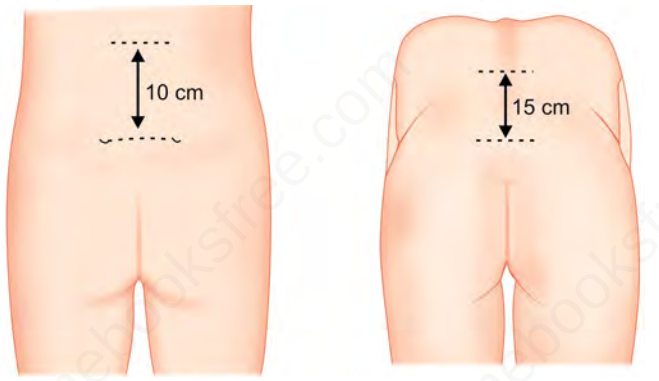


Fig. 8: The schober text detects reduced flexion. With the patient standing mark the skin overlying the fifth lumbar spinous process (usually at the level of the posterior superior iliac spine or the dimple of venous) and also loom above. On forward flexion, this should increase to >15 cm

may reveal muscle spasm and loss of normal lordosis with positive Schober test (Fig. 8). There is slow forward bending of spine (Fig. 9).

Figure 16.4 The Schober test detects reduced flexion. With the patient standing mark the skin overlying the fifth lumbar spinous process (usually at the level of the posterior superior iliac spine or the dimple of Venous) and also 10 cm above. On forward flexion, this should increase to > 15 cm.

Peripheral joint involvement – Inflammatory disease of hip (Fig. 10) and shoulder may produce progressive disability.

Enthesopathic features include plantar fasciitis, costochondritis and Achilles tendinitis.

Extraarticular manifestations include acute anterior uveitis, IBD, aortic insufficiency.

Investigations

(a) *Radiology* – demonstrates sacroiliitis. Early change in lumbar spine is manifested as squaring of the superior and inferior margins of vertebral body (Fig. 11); later change results in bamboo spine (Figs. 12 to 14). Hip arthritis is seen frequently (Figs. 15 to 17).

(b) *Laboratory tests* – (i) ESR is elevated in 50%. (ii) Serum IgA may be elevated. (iii) Serum creatinine phosphokinase and alkaline phosphatase may be slightly raised. (iv) HLA-B27 is present in 95%.

Management

(a) *Physiotherapy* has a major role in long-term management. (b) *Pharmacotherapy* as in treatment of RA. (c) *DMARDs* – Sulfasalazine and methotrexate appear to have an effect only in patients with peripheral joint

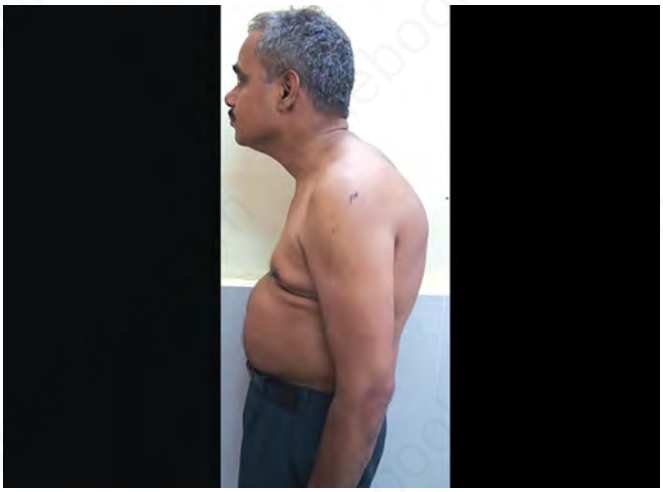


Fig. 9: AS forward bending

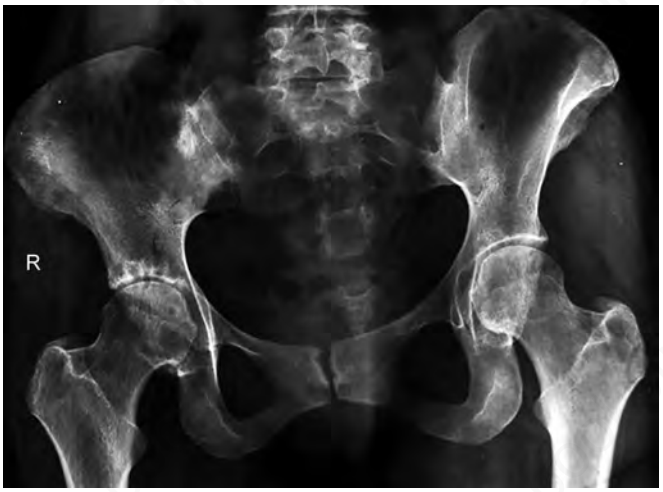


Fig. 10: X-ray AS with bilateral hip arthritis and bilateral sacroiliitis

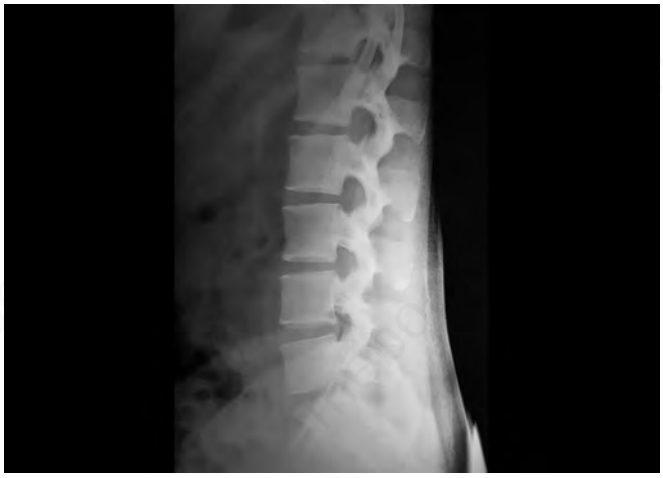


Fig. 11: AS X-ray spine showing anterior shining edges of lumbar vertebrae

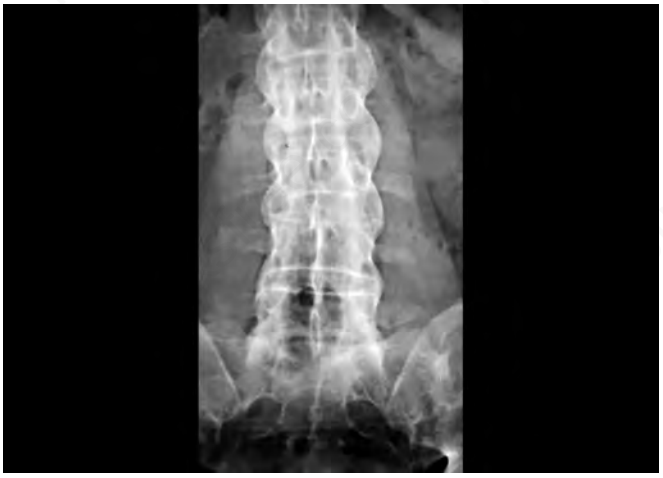


Fig. 12: Bamboo spine AP view in AS

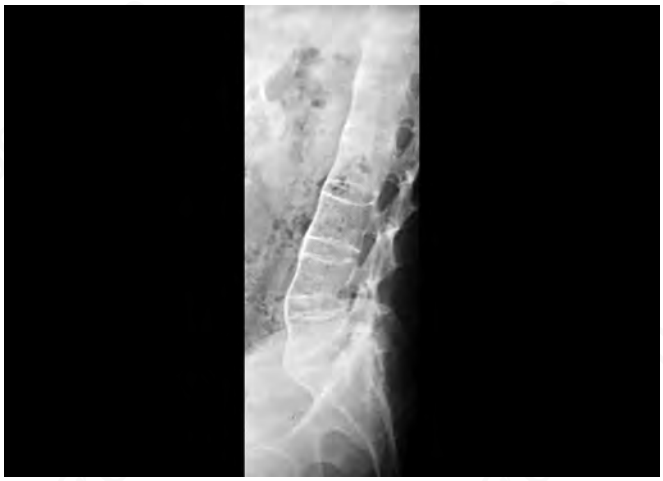


Fig. 13: Bamboo spine lateral view in AS

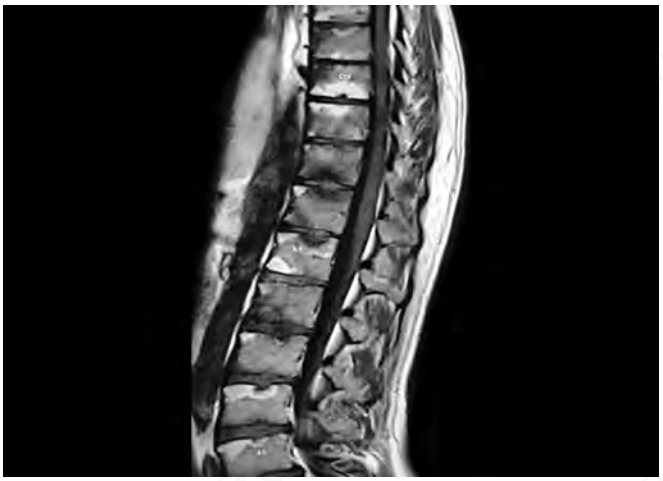


Fig. 14: AS MRI showing marrow oedema

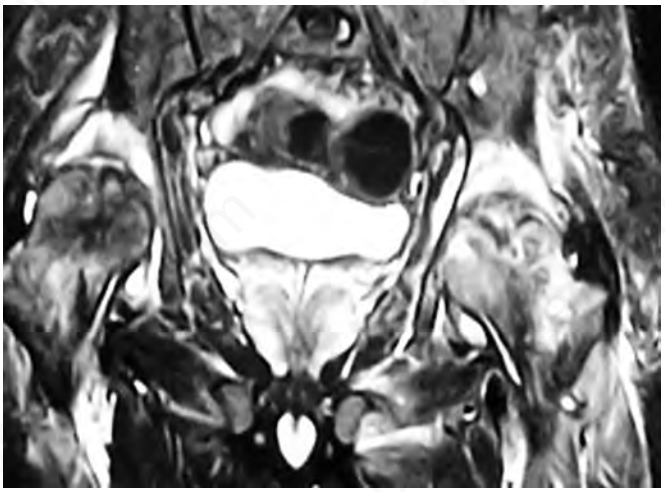


Fig. 15: Bilateral hip arthritis in AS on MRI

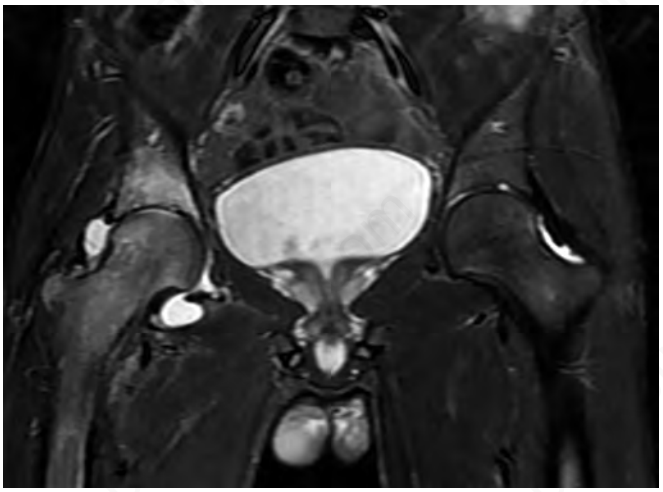


Fig. 16: Right hip arthritis MRI

Fig. 17: Bilateral hip arthritis on X-ray

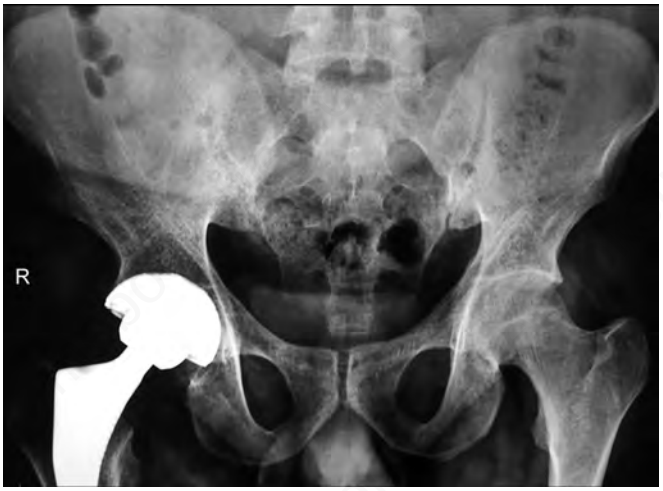


Fig. 18: THR done in AS

involvement. (d) Anti-TNF α agents- Infliximab is given intravenously—3-5 mg/kg body weight and then repeated 2 weeks later, again 6 weeks later and then at 8-week intervals. Etanercept 50 mg s.c. once weekly, Adalimumab 40 mg s.c. biweekly. Golimumab 50 or 100 mg s.c. every 4 weeks. Certolizumab pegol 400 mg s.c. every 4 weeks. (d) *Bisphosphonates* may act on both the underlying osteoporosis and inflammatory disease itself. (e) *Pulsed i.v. methylprednisolone* 0.5 g on one or more occasions, may have a short-term effect allowing patient to get more benefit from physiotherapy and hydrotherapy. (f) *Surgery* is most often used in patients with advanced hip involvement (Fig. 18).

POST-INFECTIVE ARTHRITIS

Arthritis that follows an identifiable infection but does not have the characteristics of joints sepsis may be considered post-infective.

Reiter's syndrome is an episode of peripheral arthritis of more than 1 month's duration occurring in association with urethritis or cervicitis. It is a spondyloarthropathy and is associated with many bacterial GI, genitourinary and possibly respiratory infections.

Aetiology

(a) *Trigger infections* – Reactive arthritis occurs particularly during outbreaks of enteritis caused by *Salmonella,*

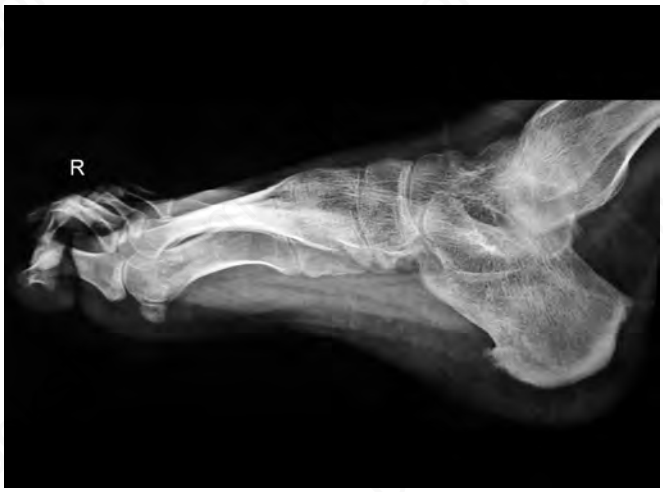


Fig. 19: X-ray calcaneal spur

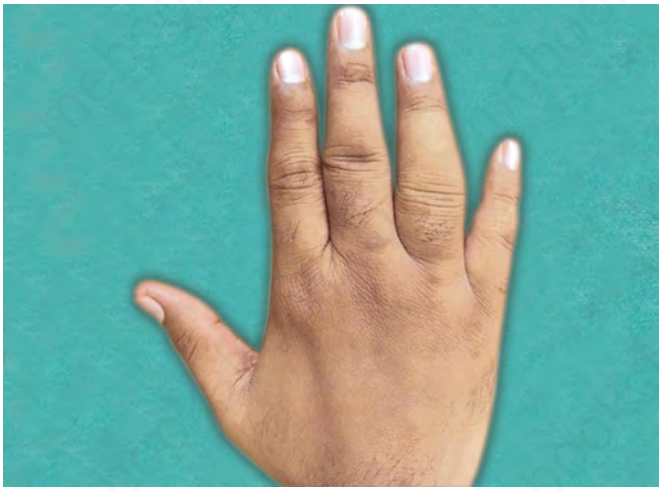


Fig. 20: Sausage digit on Rh 4th digit

Campylobacter, Yersinia or *Shigella.* About 1% of cases of non-gonococcal genital tract infections are complicated by arthritis (SARA). (b) *HLA-B27* – Presence of this gene confers a 40-fold increased risk of Reiter's syndrome.

Clinical Features

Of Reiter's syndrome/reactive arthritis

- History of GI or genitourinary tract infection within the last 6 weeks
- Systemic symptoms of fever, malaise and fatigue
- Enthesitis [particularly of tendo-Achilles and plantar fascia insertions at the calcaneum (Fig. 19)] occurs in about 50%.
- Tenosynovitis at the fingers and toes, produces dactylitis or 'sausage digits' (Fig. 20).
- Acute sacroiliitis causes lower back and buttock pain.
- Psoriasiform skin and mucous membrane lesions are seen in 20% especially men. Keratoderma blennorrhagica is pustular psoriasis on soles of feet (Fig. 21). Circinate balanitis and vulvitis are also psoriasiform rashes.
- Urethritis and/or cervicitis is usually infective in SARA.
- Gut inflammation affects both small and large bowel.
- Painful red eyes occur in about 30%. This is usually conjunctivitis, but occasionally iritis occurs synchronously with arthritis.

Investigations

(a) *Blood tests* – Elevated inflammatory markers. (b) *Urinalysis* may show pyuria. (c) *Urethral or cervical smears* show purulent exudate. (d) *Arthrocentesis* can be performed to exclude septic arthritis. (e) *Urethral and/or cervical cultures* or antigen or DNA may reveal sexually transmitted pathogens such as *C. trachomatis.* (f) *Radiography* may demonstrate erosions, particularly at small joints in chronic cases.

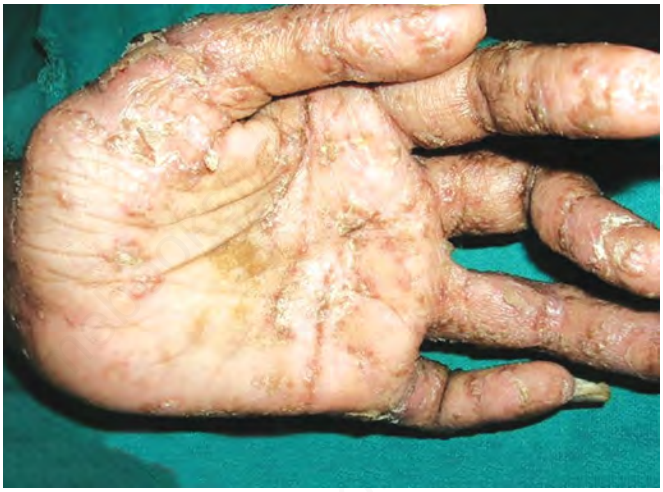


Fig. 21: Keratoderma blennorrhagica

Management – (a) Physiotherapy. (b) NSAIDs in acute, active disease; also in chronic cases sulfasalazine and methotrexate. (c) Tendinitis and enthesitis can be treated with intralesional steroids.

ACUTE RHEUMATIC FEVER

This has been discussed in Diseases of Children.

OTHER SERONEGATIVE SPONDYLOARTHROPATHIES

PSORIATIC ARTHRITIS

Most patients have skin or nail psoriasis; joint inflammation precedes psoriasis in about 15% of patients. See Table 16 for the classification criteria for psoriatic arthritis (CASPAR criteria).

Etiopathogenesis

1. *Hormonal factors* may have a modifying role–psoriatic arthritis usually improves during pregnancy and there is a postpartum flare as in RA. 2. *Immunological mechanisms* may be important as suggested by restricted clonality of T cells in both psoriatic skin and synovium and worsening of arthritis with HIV infection. 3. *Genetic factors* – up to 10% of first-degree relatives of probands with psoriatic arthritis have this condition. Results of genome mapping studies have identified several candidate genes for psoriasis that may also be implicated in arthritis (e.g. cytokines genes, corneodesmosin, MICA genes).

Patterns of Disease

Distal interphalangeal (DIP) joint disease is almost pathognomonic of psoriatic arthropathy. Similarly involvement of interphalangeal joints of the toes in addition to the hallux is only seen in psoriatic arthritis and Reiter's syndrome (Figs. 23 and 24).

Arthritis mutilans is a deforming, destructive arthritis involving the small joints of hands and feet accompanied by osteolysis of the phalanges (Fig. 22).

Peripheral oligoarthritis or polyarthritis – The greatest overlap between subgroups is seen in patients with a relative asymmetrical pattern of joint involvement initially, some of whom progress to a more symmetrical disease.

Spondylitis – About 10–15% of patients, mainly males, have principally spinal involvement with thick asymmetric syndesmophytes (Fig. 25). Cervical spine involvement is common Figures 24 and 25.

Table 16: classification criteria for psoriatic arthritis (CASPAR criteria)

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine or entheseal) with ≥3 points from any of the following five categories:
1. Evidence of current psoriasis, personal history of psoriasis or family history of psoriasis
2. Typical psoriatic nail dystrophy observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation in the hand or foot

Table 17 gives differential diagnosis of psoriatic arthritis.

Table 17: Differential diagnosis of psoriatic arthritis

Causes of oligoarthritis	*Causes of symmetrical polyarthritis*
• Osteoarthritis	Rheumatoid arthritis
• Gout	Systemic lupus erythematosus
• Reactive arthritis/	Polyarticular gout
• Early rheumatoid arthritis	

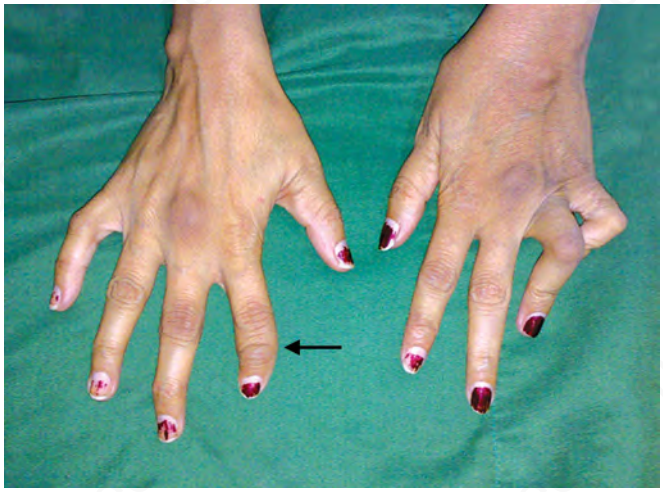


Fig. 22: Arthritis mutilans in psoriatic arthritis involving right 2nd DIP joint

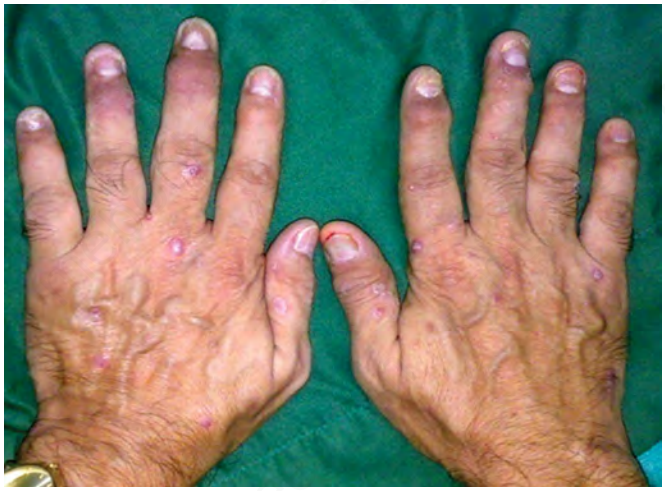


Fig. 23: PsA hand showing psoriatic skin lesions, dystrophic nails and DIP arthritis

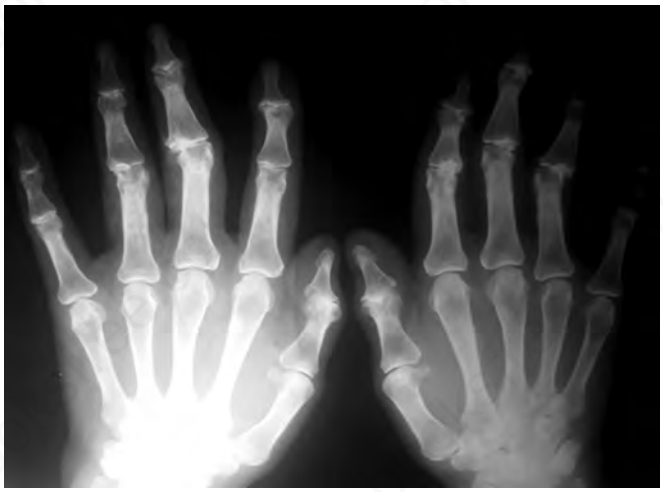


Fig. 24: PsA X-ray hand showing bilateral PIP and DIP arthritis

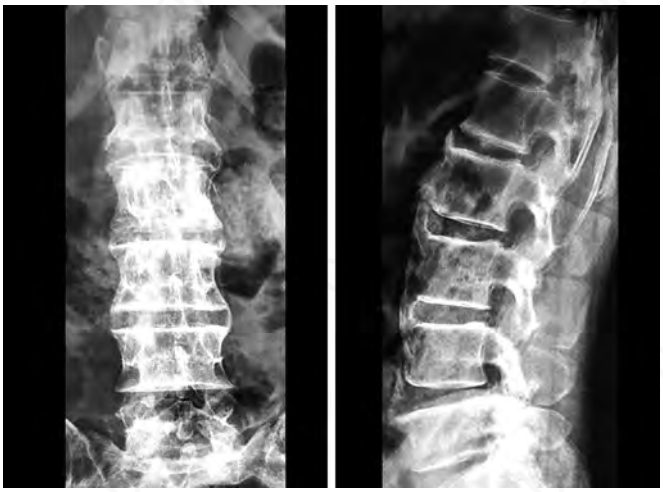


Fig. 25: PsA spine X-ray showing assymetric syndesmophytes

Radiology and Investigations in Psoriatic Arthritis

Peripheral Joints

- Lack of periarticular osteoporosis
- Osteolysis (whittling of phalanges, 'pencil-in-cup')
- Periostitis
- Ankylosis
- New bone formation within enthesis (e.g. plantar spur)

Spine

- Random asymmetrical involvement
- Paramarginal syndesmophytes
- High prevalence of cervical spine disease
- Sacroiliitis may be asymmetrical

Laboratory Tests

- Absence of rheumatoid factor
- Elevated ESR, C-reactive protein, plasma viscosity
- Sterile synovial fluid with modest increase in neutrophils

Management

NSAIDs are necessary initially, occasionally analgesics alone suffice. Sulfasalazine or low dose methotrexate (up to 15 mg/week) are added in patients with persistent peripheral joint synovitis. Antimalarials are avoided because of the acute psoriatic skin reaction. Newer agent Ustekinumab, a monoclonal antibody to the shared IL-23/IL- 12 p40 subunit, is found efficacious.

SAPHO

Palmoplantar pustulosis is associated with a form of arthritis that affects the anterior chest wall (particularly the sternoclavicular and acromioclavicular joints). The 'SAPHO' (synovitis, acne, pustulosis, hyperostosis of the spine and osteitis) is used to describe some of the characteristic features of the condition, which seem to overlap with psoriatic arthritis. It has a chronic but benign course and usually responds to NSAIDs.

ENTEROPATHIC ARTHRITIS

Peripheral oligoarthritis usually affecting the lower limb accompanies inflammatory bowel disease in about 10% of patients. Other extraintestinal manifestations (e.g. uveitis, erythema nodosum, pyoderma gangrenosum) are more common in patients with arthritis and occur more often in Crohn's disease than in ulcerative colitis. Non-erosive, asymmetrical synovitis affecting the knee or ankle is the most common presentation. NSAIDs are avoided because of risk of further bowel aggravation. Corticosteroid injection of affected joints can be used in combination with sulfasalazine in persistent synovitis. Methotrexate is useful in erosive disease.

Spondyloarthritis and sacroiliitis is also seen in association with inflammatory bowel disease, its course is independent of the bowel inflammation. HLA-B27 is positive in about 60–70% of patients.

JUVENILE IDIOPATHIC ARTHRITIS

Complications

- Chronic anterior uveitis, oligo-articular onset in young female.

  Growth: (a) Generalized (from chronic disease, use of corticosteroids) (b) Localized - (i) Overgrowth. (c) Leg-length discrepancy because of active knee synovitis. (d) Undergrowth because of premature fusion of epiphysis (e.g. micrognathia)
- Constitutional - Anemia, fever, weight loss
- Osteoporosis - Due to poor mobility, corticosteroids, poor dietary intake of calcium, vitamin D.
- Amyloidosis especially in severe systemic onset JIA
- Joint failure particularly with polyarticular disease
- Psychosocial, educational impact

Subtypes of JIA

1. Oligoarticular onset the most common type has the best prognosis.
2. Psoriatic arthritis in adults, more common in girls.
3. Enthesitis-related often presents with oligoarthritis, most commonly in large joints of lower limbs. Axial spine involvement is uncommon at presentation in childhood but a significant number have sacroiliitis and ultimately ankylosing spondylitis.
4. Polyarticular JIA affects more than 5 joints during the first 6 months of disease with symmetrical involvement of small and large joints.
5. Systemic-onset - JIA can occur at any age, equally common in males and females, as acute illness with fever, rash, lymphadenopathy, hepatosplenomegaly and occasionally carditis. About one third of children develop severe polyarthritis.

Table 18: Juvenile idiopathic arthritis (JIA). Classification:

Age at onset	*<16 years*
Minimum duration of arthritis	*6 weeks*
Subtypes	*Clinical features*
1. Systemic	Arthritis, fever, rash
2. Oligoarthritis – Persistent – Extended	1–4 joints affected during first 6 months Affected < 4 joints throughout course Affected > 4 joints after first 6 months
3. Polyarthritis – Rheumatoid factor negative – Rheumatoid factor positive	 – Affects > 5 joints in first 6 months – Affects > 5 joints in first 6 months
4. Enthesitis-related arthritis	Arthritis and enthesitis or arthritis with at least two of sacroiliac tenderness, inflammatory back pain, HLAB27+, family history of HLAB27-related disease
5. Psoriatic arthritis	Arthritis and psoriasis, at least two of dactylitis, nail changes, family history of psoriasis
6. Other	Arthritis of unknown cause or not fulfilling above categories

Complications of Juvenile Idiopathic Arthritis

Chronic anterior uveitis: Highest risk – Oligo-articular onset JIA, young female (< 6 years), antinuclear antibody positive, within 2 years of onset of arthritis.

Growth

- Generalized (chronic disease, use of corticosteroids)
- Localized
- Overgrowth (e.g. leg-length discrepancy because of active knee synovitis)
- Undergrowth because of premature fusion of epiphyses (e.g. micrognathia)

Constitutional

- Anemia of chronic disease
- Fever, weight loss, malnutrition

Osteoporosis

Due to poor mobility, corticosteroids, poor dietary intake of calcium

Amyloidosis

Uncommon – principally in systemic-onset JIA

Joint Failure

Particularly patients with polyarticular disease and those with positive rheumatoid factor

Psychosocial and Educational Impact

- Depression, social isolation, unemployment more common
- Impact on the family (parents and siblings)

4. JOINT AND BONE INFECTIONS

BACTERIAL INFECTIONS

Specific bacteria may be associated with septic arthritis, osteomyelitis and triggering of reactive arthritis. Patients with RA are at greater risk of septic arthritis.

Gonococcal arthritis – is now uncommon. Presentation is usually with diffuse or migratory arthralgia and low-grade fever, or isolated monoarthritis or oligoarthritis may occur.

Brucellosis – Infection of the joints is the most common form of localized disease. The arthritis is usually monoarticular affecting large peripheral joints, sacroiliac joints and the spine.

Tuberculosis – Five clinical syndromes of articular tuberculosis are – Spondylitis (Pott's disease), peripheral arthritis, osteomyelitis/dactylitis, tenosynovitis/bursitis and reactive arthritis (Poncet's disease) in which knees, ankles and elbows are more commonly involved.

Leprosy – Three syndromes may develop – arthralgia/arthritis with or without erythema nodosum leprosum, swollen hand syndrome and vasculitis.

VIRUS INFECTIONS

Some viral infections are accompanied by arthritis more often than others.

Rubella arthritis and arthralgia may occur in up to 50% of infected women as compared with up to 60% men. Live virus and viral antigens have been detected in synovial fluid. Arthritis occurs within one week of the rash. Fingers, wrists, elbows, knees, hip and toe joints are most commonly affected, usually symmetrically.

Parvovirus B19 may be associated with rheumatoid-like polyarthritis. Symmetrical polyarthritis may occur in association with erythema infectiosum.

Hepatic viruses – Transient polyarthritis occurs in 30% of patients during the prodromal stage of acute hepatitis B. Small joints are usually affected.

Musculoskeletal presentations in *HIV infection* are listed in Table 19.

Chikungunya fever. The osteoarticular problems usually subside in 2 to 3 weeks' time. The wrists and small joints of the hands and wrists are worst affected. Major joints like knee and shoulder and spine can also be involved.

Table 19: Musculoskeletal presentations in HIV infection

Arthralgia intermittent, mild and polyarticular
HIV-arthritis commonly affects the knees and ankles and lasts from hours to a few days
Reiter's syndrome
Psoriatic arthritis
Avascular necrosis of bone (may be associated with cardiolipin antibodies)
Septic arthritis (usually caused by *Staph. aureus* or *Strep. pneumoniae*)
HIV patients can develop RA

In approximately 20% cases, they disappear after a gap of few weeks. In less than 10% cases, they tend to persist for months. In about 10% the swelling disappears, pain subsides, but only to reappear with every other febrile illness for many months. Each time the same joints get swollen, with mild effusion. Destroyed metatarsal head has been observed in patients with persistent joint swelling. The classical bending phenomena is due to lower limb and back involvement which forces the patient to stoop down and bend forwards.

PARASITIC INFECTIONS

Parasitic arthritis may be caused by (a) localization of the parasite in the joint, (b) reaction to presence of parasite in neighbouring tissues, (c) secondary to an immune-mediated response to parasite antigen/products released spontaneously, (d) occur following treatment.

Clinical Features of Septic Arthritis

It is more common in children, the elderly and immunosuppressed individuals (e.g. AIDS patients, stem cell implant recipients, patients taking immunosuppressive agents, those with damaged joints). The hip and knee are most commonly involved. H. influenzae is a common cause of haematogenous arthritis in children aged between 1 months and 5 years.

The inflammatory process causes the joint to become swollen through synovial membrane proliferation. Levels of enzymes within the synovial fluid (e.g. elastase, collagenase) increase and the total effect is to degrade cartilage.

Diagnosis of suspected joint infection:

1. *Blood tests*: (a) Raised ESR and CRP. (b) Immune tests (e.g. IgM and IgG antibodies to parvovirus 19). (c) Blood cultures.
2. *Imaging:* Radiographic changes indicate that an infection has been present for more than 2 weeks.
3. *Microbiology:* Synovial fluid culture, microscopic smears and arthroscopy or open synovial biopsy may be negative in 30% of M. tuberculosis infections. Mantoux test may be positive in tuberculous infection.

Management: Early therapy with appropriate antibiotics. Abscesses should be drained, because decompression prevents further obstruction of blood vessels and resulting bone necrosis.

Palindromic Rheumatism

Periodic monoarticular or polyarticular joint swelling, "recurring arthritis", attacks last from hours to days, clear spontaneously and leave no joint residuals. Thirty to forty per cent of these cases develop rheumatoid arthritis.

Juvenile Rheumatoid Arthritis (Still's Disease)

Acute form of rheumatoid arthritis occurring usually between ages of 2 and 4 years. Certain features are quite distinct from adult disease – more frequent occurrence of high fever, characteristic rash, splenomegaly, lymphadenopathy, chronic iridocyclitis, single-joint involvement, failure to grow, striking leucocytosis, and infrequency of subcutaneous nodules. Negative rheumatoid factor.

Intermittent Hydrarthrosis

A joint disorder most common in the knees, occurs at regular cyclic intervals. The synovitis is acute, lasts for 2 days to 4 weeks and clears without residuals. Many of these patients eventually develop typical signs of rheumatoid arthritis.

5. OSTEOARTHRITIS

Osteoarthritis is an abnormality of synovial joints characterized by softening, splitting and fragmentation (fibrillation) of articular cartilage not attributable to direct contact with inflammatory tissue. This is usually accompanied by subchondral sclerosis and bone cysts, joints space narrowing and bony overgrowths at tissue joint margins (osteophytes).

AETIOLOGY

a. *Age* is a major risk factor
b. *Race* – Hip OA is less common in Chinese and Asians than in those of Western origin, whereas knee osteoarthritis is more common in Afro-Carribbeans.
c. *Genetic predisposition* – Clinical evidence of inheritance of OA:
   - Heberden's nodes are more common in sisters of affected women than in the general population.
   - 20% of individuals with osteoarthritis have a positive family history
   - First-degree relatives are at a twofold risk of generalized radiological osteoarthritis
   - There is greater concordance in identical twins at several joint sites
   - Heritability of radiological knee and hand osteoarthritis is 40–65%
d. *Gender and hormonal factors* – Below 45 years, the disease is in men, in whom it usually involves one or two joints. Above 55 years, it is more common in women, usually involving several joints (particularly interphalangeals, first metacarpal and knees).
e. *Obesity* – The relationship is stronger in women than in men and is strongest at the knee.
f. *Other systemic factors* – In women a significant association between hand disease and elevated serum cholesterol levels. Hypertension has been associated with generalized osteoarthritis in men and knee osteoarthritis in non-obese women. Trauma is associated with development of osteoarthritis.

Pathogenesis – OA is a disease of both articular cartilage and subchondral bone. The disease is characterized by progressive degradation of the components of extracellular matrix of the articular cartilage associated with secondary inflammation factors and increased bone turnover and repair.

Clinical features – OA is characterised by gradual development of joint pain, stiffness, limitation of movement and swelling, which may be caused by synovitis with effusion or from osteophyte formation (as in Heberden's nodes). The bony enlargement that accompanies osteophyte formation may lead to joint deformity (Figs. 26 and 27).

Generalized OA refers to involvement of at least three joints or a group of joints (e.g. interphalangeal joints).

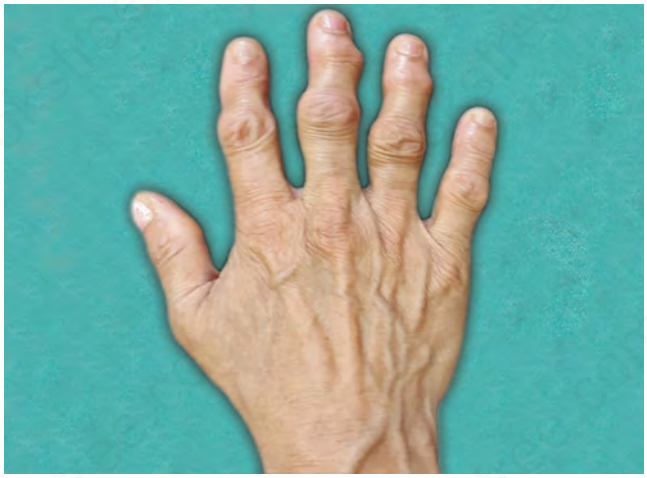


Fig. 26: OA hand showing Heberden's nodes

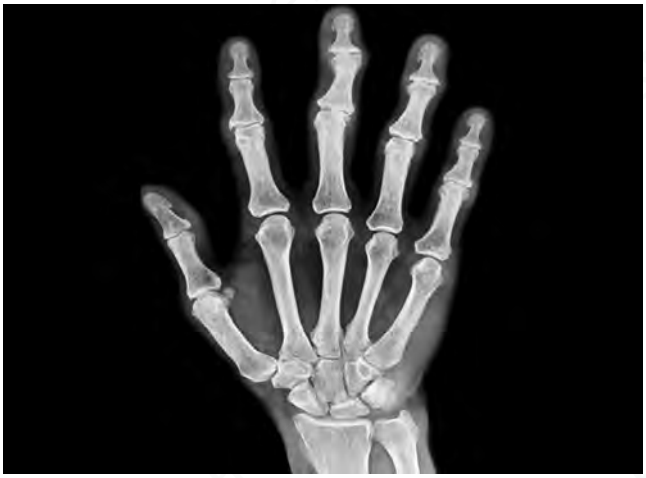


Fig. 27: OA hand X-ray showing DIP arthritis

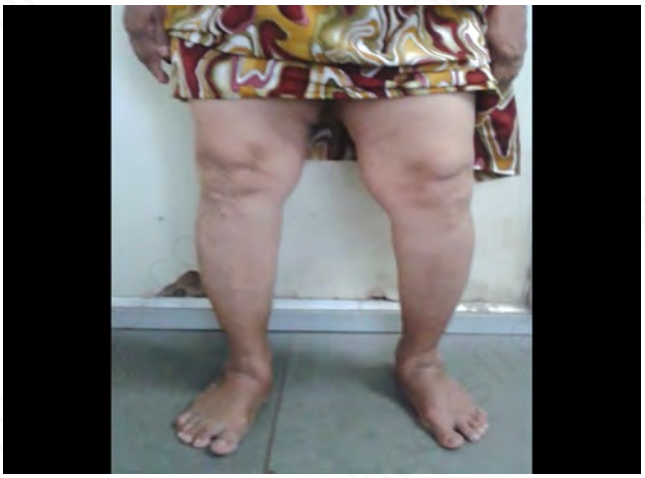


Fig. 28: OA knees bowing legs

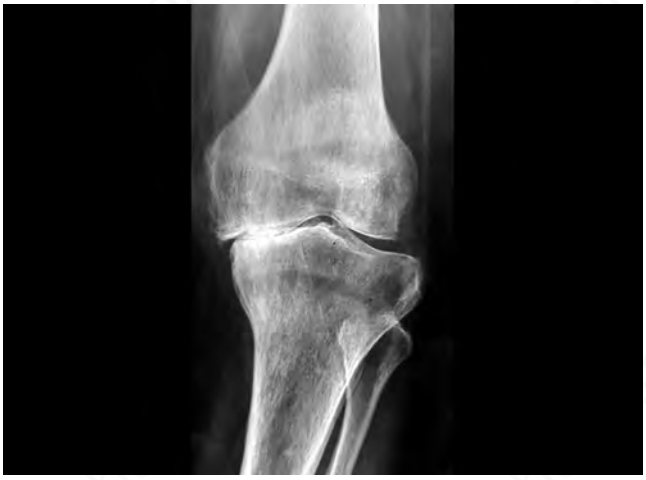


Fig. 29: OA knees X-ray showing decreased medial joint space and erosions

There are two types nodal and non-nodal – The nodal type features Heberden's nodes of the interphalangeal joints, predominates in women and exhibits a strong tendency to familial transmission.

Hands – Limitations of activity that require dexterity (e.g. dressing, feeding) are affected.

Hip disease – First sign is usually pain or restriction of internal rotation followed by pain on flexion.

Knee – Tibiofemoral arthritis is usually bilateral and is associated with early morning stiffness and pain on weight bearing particularly on climbing stairs. Night pain is a sign of severe disease. In elderly patients, knee effusions and crepitus are common. Severe OA of the knee joints leads to valgus deformity of the joints (Fig. 28).

RADIOLOGY

OA knee shows reduced medial joint space with osteophyte formation (Fig. 29).

MANAGEMENT

Non-surgical treatment

Pharmacological

- Analgesics and anti-inflammatory treatment – Simple analgesics the appropriate first-line treatment for uncomplicated osteoarthritis e.g. paracetamol 4g/day. COX-2 specific agents have a better safety profile than NSAIDs. Tramadol is a centrally acting oral analgesic with efficacy similar to ibuprofen.
- Intraarticular therapies – Intraarticular glucocorticoids are used in treatment of knee osteoarthritis when pain and swelling persist despite drugs such as NSAIDs, and may temporarily relieve symptoms.

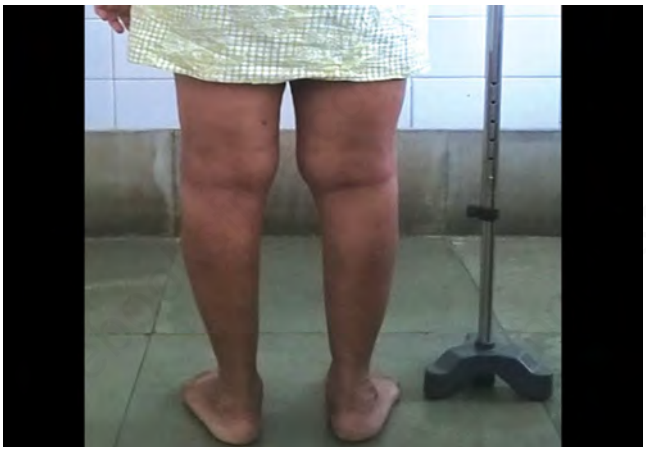


Fig. 30: OA knee postoperative with TKR done

- Chondroprotective agents – Glucosamine and chondroitin have been shown to modify symptoms to a degree equivalent to anti-inflammatory agents.

Non-pharmacological

- Self-management programmes
- Weight reduction
- Physiotherapy
- Occupational therapy
- Aids (e.g. shoe wedges, patella-taping, cushioned training shoes, stick)

Surgery

Arthroplasty is successful in both hip and knee disease. Osteotomy relieves pain and can stimulate fibrocartilaginous healing of the joints. Nowadays total knee replacement is a preferred modality (Fig. 30).

6. METABOLIC AND CRYSTAL ATHROPATHIES

GOUT

Gout is the term used to describe the constellation of clinical features that result from deposition of microcrystals of sodium urate monohydrate or uric acid from hyperuricemic body fluids. These include acute arthritis, tenosynovitis, bursitis or cellulitis, tophaceous deposits, renal disease and urolithiasis.

PATHOGENESIS

In all populations, serum urate concentration is the major determinant of risk of developing gout.

Uric acid is the end product of purine metabolism in humans, who lack the enzyme uricase (which degrades uric acid to allantoin in most animals). The miscible body pool of urate in normal individuals is about 1 g, and about 60% of this is replenished daily from catabolism of newly synthesized and dietary proteins. Two-third of urate formed each day is excreted by the kidneys and one-third from GI tract.

Genetic and environmental factors lead to gout and hyperuricemia by reducing excretion of uric acid (90%) (Table 20) and/or increased production of uric acid (10%) (Table 21).

The inherent metabolic aberration in gout is hyperuricemia which is defined as an elevation in serum urate (SUA) level ≥ 6.8 mg/dL.

Table 20: Causes of reduced renal excretion of uric acid

Primary	*Secondary*
Reduced fractional urate clearance	*Reduced fractional urate clearance*
• Idiopathic	• Hypertension
• Familial juvenile gouty nephropathy	• Hyperparathyroidism
	• Myxoedema
	• Down's syndrome
	• Increased levels of organic acid (e.g. exercise, starvation, alcohol, ketoacidosis)
	• Lead nephropathy
	• Sarcoidosis
	• Bartter's syndrome
	• Beryllium poisoning
	Drug administration
	• Diuretics (therapeutic dose)
	• β-blockers
	• Angiotensin-converting enzyme inhibitors
	• Salicylates (low dose)
	• Pyrazinamide
	• Ethambutol
	• Nicotinic acid
	• Cyclosporine (particularly following organ transplantation)
	• Reduced renal functional mass
	• Chronic kidney disease
	• Reduced glomerular filtration rate
	• Volume depletion
	• Nephrogenic diabetes insipidus

Table 21: Causes of increased uric acid production

Primary	*Secondary*
Increased purine synthesis de novo	*Increased purine synthesis de novo following increased catabolism of purine nucleotides*
• Idiopathic	• G6PD deficiency (glycogen storage disease type I)
• Hypoxanthine-guanine phosphoribosyl transferase deficiency	• Myogenic (glycogen storage type III, V, VII)
• Phosphoribosyl pyrophosphate synthetase overactivity	• Hereditary fructose intolerance (aldolase B deficiency)
• Ribose-5-phosphate overproduction	*Increased turnover of preformed purines*
• AMP-deaminase deficiency	• Lymphoproliferative and myeloproliferative disorders
	– Hodgkin's disease
	– Leukaemia
	– Lymphosarcoma
	– Myeloma
	– Polycythaemia rubra vera
	– Waldenstrom's macroglobulinemia
	• Cytotoxic drugs
	• Carcinomatosis
	• Gaucher's disease
	• Chronic haemolytic anaemias
	• Secondary polycythemia
	• Severe exfoliative psoriasis

CLINICAL FEATURES

The natural history of gout has four stages:

1. ***Asymptomatic hyperuricemia***
2. ***Acute gout*** - may be precipitated by many factors (Table 22).

Table 22: Precipitating causes of gout

• Trauma
• Unusual physical exercise
• Surgery
• Severe systemic illness
• Severe caloric restriction
• Dietary excess
• Alcohol
• Drugs
• Diuretics Initiation of uricosuric or allopurinol therapy Initiation of B12 therapy in pernicious anaemia Following drug allergy Cytotoxic drug therapy

First attack occurs commonly in men aged 30–60 years, usually monoarticular, the metatarsophalangeal joint of the great toe is the first joint affected in 70%. Acute gouty arthritis can occur in ankles, knees, wrists, elbows and small joints of hands and feet; it seldom occurs in axial skeleton or large joints such as the hip and shoulder. Acute gout can also present as tenosynovitis, bursitis or cellulitis.

The initial attack may be sudden. The affected joint becomes hot, red and swollen with shiny overlying skin and is extremely painful and tender. Very acute attacks may be accompanied by fever, leucocytosis and raised ESR.

First attacks are seldom associated with residual disability, but recurrent attacks are followed by progressive cartilage and bone erosion, deposition of tophi, secondary osteoarthritis and disability associated with permanent restriction of joint function.

3. ***Intercritical gout*** – Variable symptom-free periods between acute attacks; with progressive shortening of the intercritical period between attacks.
4. ***Chronic tophaceous gout*** – inevitably follows recurrent attacks and is characterized by asymmetrical joint swelling (Figs. 31 and 32). Tophi (massive accumulations of microcrystals of uric acid and amorphous urates surrounded by histiocytes, giant cells and fibrosis) develop in periarticular tissues, cartilaginous helix of the ear, bursae and tendon sheaths. CT and MRI have revealed tumour-like masses of tophi in patients with gout and carpal tunnel syndrome, and in the spine in some patients. Rarely tophi form in the eye, tongue, larynx or heart, and interference with cardiac conduction and valvular function has been recorded.

   Tophus formation is related to serum uric acid and to local factors. Tophi seldom develop in individuals with asymptomatic hyperuricemia; however they may develop rapidly in feet or hands of post-menopausal women with heart failure and renal insufficiency who develop acute or subacute gouty arthritis following prolonged diuretic administration.

DIAGNOSIS

- Sudden onset of acute inflammatory monoarthritis, particularly in foot or ankle
- Onset following provoking event
- One or more previous episodes of self-limited acute arthritis followed by periods completely free of symptoms
- History of renal colic or nephrolithiasis
- History of hypertension or renal disease
- Family history of gout, hyperuricemia, nephrolithiasis or renal disease

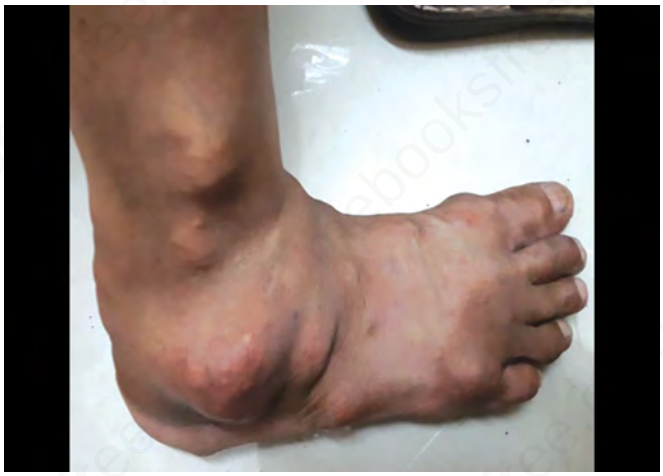


Fig. 31: Gout foot

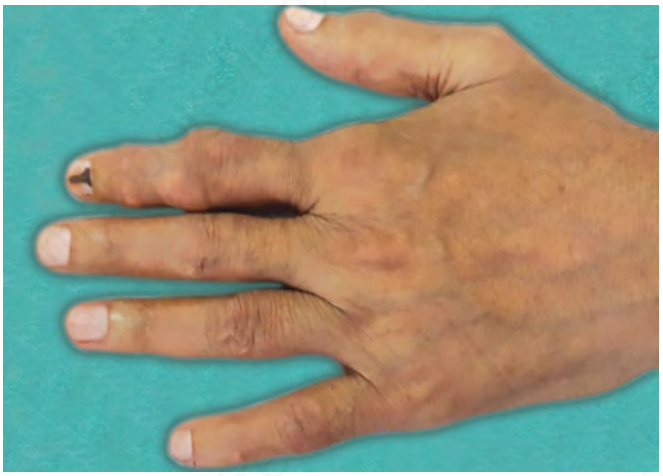


Fig. 32: Gout hand

Table 23: Differential diagnosis of gout

Acute
• Infective arthritis
• Bursitis, cellulitis, tenosynovitis
• Other crystal arthropathy
• 'Pseudogout' caused by calcium pyrophosphate
• Apatite or brushite arthritis or periarthritis
• Traumatic arthritis
• Haemarthrosis
• Rheumatoid arthritis with palindromic rheumatism
• Reactive arthritis
• Spondyloarthritis with peripheral joint involvement
• Psoriatic arthritis
• Sarcoid arthritis
• Rheumatic fever
Chronic
• Nodular RA
• Psoriatic arthritis
• Osteoarthritis with Heberden's and Bouchard's nodes
• Sarcoid arthritis
• Xanthomatosis

Diagnosis is supported by:

- Raised serum uric acid
- Characteristic radiological changes (soft tissue swelling with patchy calcification, cortical erosions of phalanges, punched-out erosions and secondary degenerative changes) in patients who have had recurrent attacks (Fig. 33).

Diagnosis is established by: Demonstration of needle-shaped, negatively birefringent crystals of monosodium urate in synovial fluid neutrophils by polarizing light microscopy. Serum uric acid levels can be normal or low at the time of an acute attack. A 24-hour urine collection for uric acid can be useful in assessing the risk of stones, elucidating overproduction or under excretion of uric acid and deciding whether it may be appropriate to use a uricosuric therapy.

Table 23 gives the differential diagnosis of gout.

MANAGEMENT

Acute Attack

NSAIDs – Any can be used but aspirin should be avoided because it causes uric acid retention unless given in very large doses.

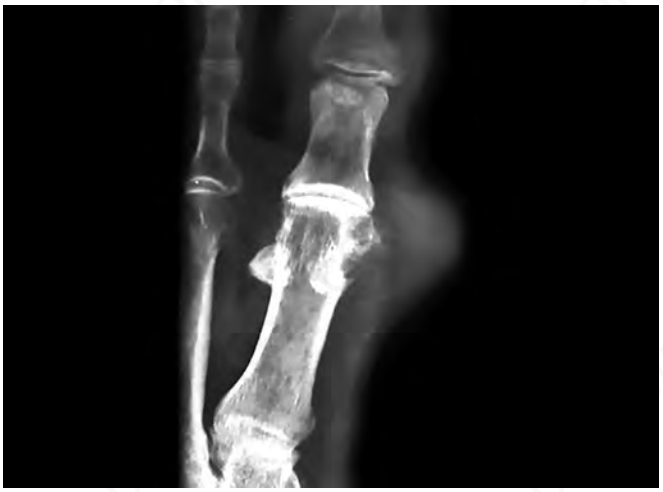


Fig. 33: Gout X-ray punched out erosions

Selective COX-2 inhibitors e.g. Etoricoxib 120 mg o.d. or Valdecoxib 20–40 mg b.d. Advantage is low risk of GI toxicity.

Colchicine 0.5 mg p.o. every 2 hours, up to 4-6 mg/day is now reserved for patients without renal, hepatic or bone marrow disease, in whom the more effective NSAIDs are contraindicated or poorly tolerated.

Corticosteroids – Intra-articular (e.g. methyl prednisolone acetate 5–25 mg per joint), systemic (oral prednisolone 20 mg/day tapered off over 4–10 days) or i.m. triamcinolone 60 mg/day repeated in 1–4 days, are highly effective, and relatively safe alternatives. In patients with acute microcrystalline synovitis in whom neither NSAID nor colchicine are recommended, e.g. elderly people and those with renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease.

Note: Allopurinol or uricosuric drugs should not be started until the acute attack has settled for 2–3 weeks, because they can prolong the acute attack or trigger further episodes. Patients should be advised to avoid diuretics and/or salicylates.

Long-term management with drugs that lower serum urate: Indications –

- Recurrent attacks
- Evidence of tophi or chronic gouty arthritis
- Associated renal disease
- Young patient with high serum uric acid and family history of renal or heart disease.
- Normal levels of serum uric acid cannot be achieved by lifestyle modifications (gradual weight loss, and restriction of alcohol and food with high purine content).

Uricosuric Drugs

Allopurinol – is the drug of choice. It lowers serum uric acid by inhibiting xanthine oxidase, which is responsible for conversion of xanthine and hypoxanthine to uric acid. Kidney function should be checked before the drug is started. Dose: 300 mg daily, with an NSAID or colchicine 0.5 mg b.d., to avert breakthrough attacks of acute gouty arthritis that often follow initiation of hypouricemic therapy. Lower doses if renal function is impaired.

Febuxostat is a nonpurine selective inhibitor of xanthine oxidase (XO) that reduces serum uric acid. Dosage – Starting dose is 40 mg od to reduce and maintain SUA level below 6 mg/dL (357 µmol/L). If SUA is >6 mg/dL after 2–4 weeks treatment with the drug 80 mg/day, the dose is increased to 120 mg/day. Gout flares may appear after initiation of Febuxostat due to changing uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis (NSAID or colchicine) is recommended upon initiation of Febuxostat. The drug is contraindicated in patients being treated with xanthine oxidase substrates azathioprine, mercaptopurine or theophylline.

Probenecid 0.5–1 g b.d., or sulfinpyrazone 100 mg t.d.s. as an alternative to allopurinol with colchicine if renal function is not impaired. Contraindications: (a) Gout with overproduction of uric acid and gross uricosuria. (b) Patients with kidney failure. (c) Presence of urate urolithiasis.

Benzbromarone 100 mg daily in those with moderate renal impairment when other uricosuric agents are ineffective and there is allopurinol hypersensitivity.

Pegloticase is a pegylated uricase, now available for patients who do not tolerate or fail full dose of other treatments. It is given intravenously usually at 8 mg every 2 weeks and can dramatically lower serum uric acid.

Asymptomatic hyperuricemia does not require prophylactic treatment in absence of a history, family history or clinical evidence of gout. Causes of secondary hyperuricemia should be sought.

Management of hypertension – Angiotensin receptor blocker losartan, which has uricosuric effect, instead of ACEIs, which cause uric acid retention.

Manifestations of Gout in the Urinary Tract

Urolithiasis – is common in hot climates.

Chronic urate nephropathy – results from a variable combination of renal tubular obstruction, tophus formation, hypertension, glomerulosclerosis and secondary pyelonephritis. In case of untreated gout and prolonged hyperuricemia it usually follows treatment of leukaemia or lymphoma with cytotoxic drugs.

Acute crystal nephropathy – can result from precipitation of uric acid in the collecting ducts with secondary tubular blockage. It usually follows treatment of leukaemia or lymphoma with cytotoxic drugs.

Familial juvenile hyperuricemic nephropathy is AD inherited disorder in which hyperuricemia is associated with decrease in fractional urate clearance.

Patients may present with gout in childhood, and renal failure usually develops in 20–40 years.

Other Clinical Associations

Metabolic syndrome – Gout and hyperuricemia are often associated with obesity, hypertension, IHD, raised plasma glycerides and low levels of LDL.

Gout with overproduction of uric acid – In absence of significant renal impairment, such patients are hypersecretors of uric acid, i.e. 24 hr urine uric acid > 600 mg (3.6 mmol) on a purine-free diet. Specific enzyme defects resulting in an increase in *de novo* purine synthesis should be suspected:

- In absence of disorders resulting in increased turnover of purines
- When gout develops before age of 20
- Family history of gout commencing at early age
- Uric acid lithiasis is the presenting feature

Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency – Lesch-Nyhan syndrome is an uncommon, x-linked recessive inborn error of metabolism in which gout and severe overproduction of uric acid are associated with choreoathetosis, variable degree of mental deficiency and compulsive self-mutilation. The enzyme defect can be detected in RBC lysate, female carriers can be identified from skin fibroblast cultures or hair root analysis and prenatal detection by using amniotic fluid cells.

Phosphoribosyl pyrophosphate synthetase super-activity is an x-linked disorder associated with severe gout, renal calculi and variable neurological disturbance.

G6PD deficiency – Children with glycogen storage disease (GSD) type I (Von Gierke's disease) who survive to adult life develop severe gout and hyperuricemia as a consequence of impaired uric acid excretion secondary to lactic acidosis and ketonaemia and increased *de novo* purine synthesis. The enzyme defect can be detected only in the liver, kidney or intestinal mucosa.

Myogenic hyperuricemia, particularly following exercise, is a feature of GSD with primary muscle involvement (GSD types III, V and VII). Hyperuricemia results from degradation of muscle ATP.

Fructose intolerance – Ingestion and infusion of fructose are associated with hyperuricemia and accelerated purine synthesis and catabolism in normal individuals. Hyperuricemia and gout can occur in patients with hereditary fructose intolerance and aldolase B deficiency.

Infantile autism has been associated with hyperuricemia and accelerated purine synthesis, but no enzyme defect has yet been identified.

METABOLIC AND ENDOCRINE ARTHROPATHIES

Metabolic Disorders

Calcium pyrophosphate dihydrate crystal deposition arthropathy – Articular cartilage calcification caused by deposition of CPPD is more common in women. It may be asymptomatic, may occur in association with osteoarthritis or may present as acute pseudogout or associated with chronic arthritis.

Pseudogout is the most common acute monoarthritis in elderly (usually female) patients. It involves, in order of prevalence, the knees, wrists, shoulders, ankles and elbows. There is acute pain with marked tenderness and often erythema and fever. The condition develops to a peak over 6–24 hours and resolves spontaneously over 1–3 weeks. Episodes can occur intermittently over years.

Investigations – (a) Synovial fluid examination by polarizing microscopy shows typical intracellular, weakly positive, birefringent, rhomboid CPPD crystals. Synovial fluid count is elevated. (b) Blood tests – Increased ESR and plasma viscosity, CRP and leucocyte count. (c) Radiography may show chondrocalcinosis of affected joint.

Management – Anti-inflammatory drugs give relief. Intra-articular corticosteroid injection in severe cases.

Chronic pyrophosphate arthropathy – Chondrocalcinosis may be asymptomatic or may be associated with arthropathy involving knees, wrists, shoulders, elbows, hips, mid-tarsal joints, and second and third metacarpophalangeal joints. Acute attacks of pseudogout may occur.

Investigations – (a) Radiography – Calcification most commonly affects the fibrocartilage of the menisci. The articular changes are those of osteoarthritis, but there are often exuberant osteophytes. (b) Synovial fluid may show CPPD crystals.

MANAGEMENT – Weight reduction, physiotherapy, anti-inflammatory drugs and intra-articular corticosteroids.

Haemochromatosis is associated with cirrhosis, arthropathy, hypogonadism, pigmentation and diabetes. Arthropathy may be an early feature. Bony swelling and restriction of movement are typically seen in 2nd and 3rd metacarpophalangeal joints, but other joints may also be affected. There may be progressive joint damage. Radiological changes are similar to those in osteoarthritis. Diagnosis is by determination of transferrin saturation and serum ferritin concentration. *Tr.* – Regular phlebotomy, and symptomatic treatment for the arthritis.

Gaucher's disease – Most patients develop joint or bone pain which may be insidious or sudden and severe. Avascular necrosis can lead to osteoarthritis. Biopsy of bone marrow shows diagnostic Gaucher's cells.

Alkaptonuria (ochronosis) – Limitation of movement may occur at the hips, knees, and less commonly shoulders, with occasional acute inflammation. Tendons and tendon sheaths are often affected. Later, osteoarthritic radiological changes occur in the large joints, and there may be multiple intra-articular loose bodies in the knees, leading to locking.

Wilson's disease – Articular involvement occurs in up to 50% of adults. The arthropathy may be severe, leading to disability within a few years. Serum copper and ceruloplasmin are reduced and urine copper raised.

Endocrine Disorders

Diabetes Mellitus

Neuropathic arthropathy can occur in long-standing poorly controlled diabetes, leading to loss of pain sensation, proprioception and vibration sense (Charcot's joints). The foot and ankle (typically the metatarsophalangeal and tarsometatarsal joints) are most commonly affected (Figs. 34 to 36). Radiological features are diagnostic – Osteolysis is the most important, but there is also localized osteoporosis, periosteal reaction and tapering of the shafts of metatarsals and phalanges giving a 'pointed bone' appearance. Infection of joints is more common, caused by Staph. aureus.

Thyroid disease

Hyperthyroidism – Thyroid acropachy (pseudo-clubbing of nails) may rarely develop after years of treated hyperthyroidism. Long-standing excess thyroxine can lead to osteoporosis.

Hypothyroidism – Joint pain, synovial proliferation and non-inflammatory effusions occur in up to one

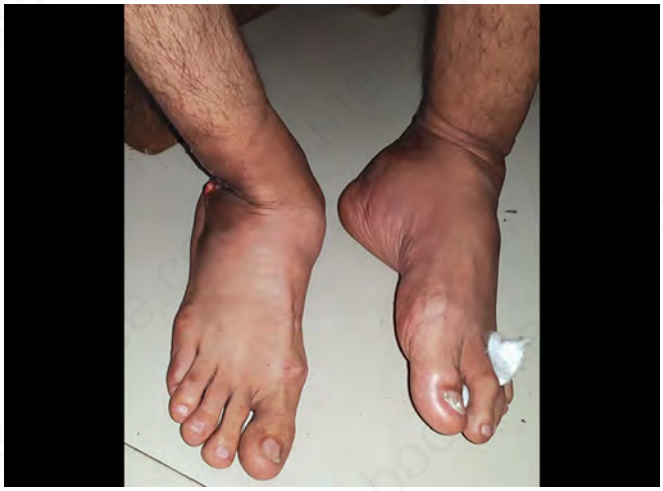


Fig. 34: Charcot foot

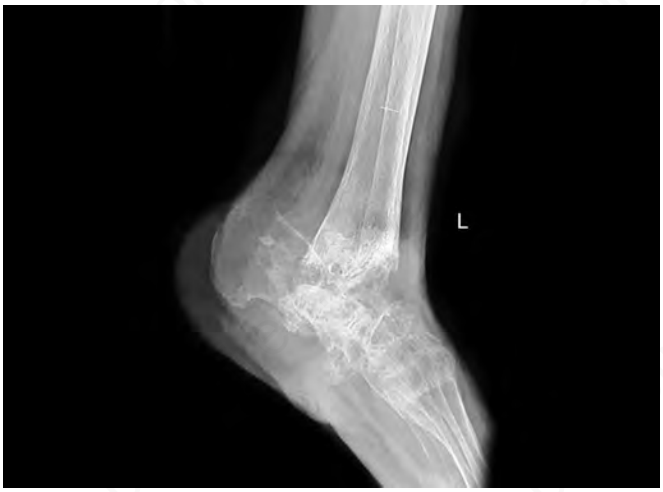


Fig. 35: Charcot foot X-ray with extensive destruction of ankle joint

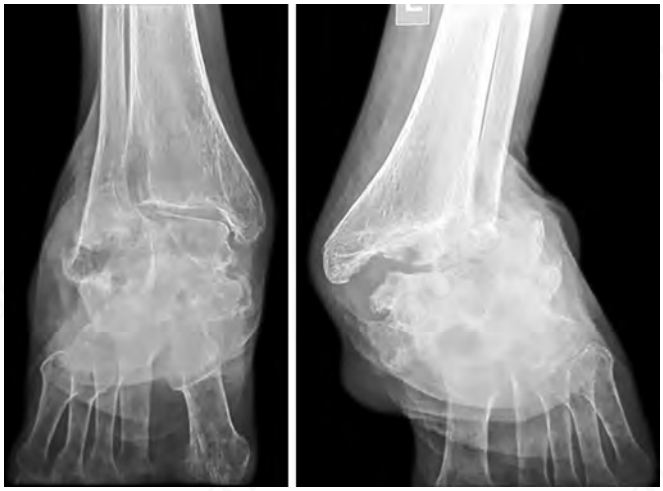


Fig. 36: Charcot foot X-ray showing destroyed ankle joint

third. Carpal tunnel syndrome occurs in about 75% of patients.

Hyperparathyroidism – Erosive arthropathy of small joints of fingers and wrists may be present. CPPD crystal deposition may occur.

Acromegaly – Joint swelling occurs as a result of synovial and bone growth; significant effusions are uncommon. Secondary osteoarthritis can develop particularly of knees and shoulders.

7. AUTOIMMUNE DISEASES

IMMUNOLOGY

Immunity is normally concerned, not only with inactivation and rejection of micro-organisms and other foreign substances but also in recognising that they are foreign. The essence of autoimmune disease is probably the failure at some point of this power of differentiating between the body's own material (self), and foreign material (not-self).

Immunological Mechanisms

Immune responses are generated by natural and adaptive mechanisms that consist of both cellular and hormonal components.

Natural immunity – is non-specific, i.e. not influenced by previous antigen-antibody interactions:

1. Phagocytic cells including polymorphonuclears, monocytes, macrophages form the cellular component of the natural immune response.
2. Natural killer (NK) cells are potent cytotoxic cells.
3. Complement system – A complex group of serum proteins, mediates inflammatory responses by attracting granulocytes and macrophages, promoting cell-cell interactions necessary for antigen processing, and stimulating lysis of enveloped viruses and bacteria.

Adaptive immunity – Humoral immunity involves production of immunoglobulins by natural B lymphocytes. Immunoglobulins are vital to immune response in 3 types:

- Immunoglobulins coat invading organisms, thereby impending their access to the host
- Immunoglobulins IgM and IgG form complement
- Immunoglobulins promote opsonization, which increases efficiency of phagocytes

IgA is the principal immunoglobulin in secreting fluids, making it the most important host defence antibody at sites of antigen entry.

Cellular immunity is mediated by T lymphocytes:

1. Subpopulation of T cells –
   - Cytotoxic (T) cells are responsible for killing cells that express foreign antigen
   - Helper T (T_h) cells enhance the activity of B cells, macrophages and inhibit activity of other cells of the immune system
   - Suppressor T (T_s) cells inhibit activity of other cells of immune system
2. Various types of antigen-presenting cells interact with T cells, stimulating release of lymphocytes, including interleukins, granulocyte macrophage colony-stimulating factors (GM-CSF), tumour necrosis factor (TNF) and interferon-α (IFN-α). These substances regulate various aspects of immune response.

Autoantibodies in autoimmune diseases. Detection of autoantibodies in the serum of patients with suspected autoimmune disease is an important part of the diagnostic process. The most widely used methods for detection of antibodies are indirect immunofluorescence (IIF) and ELIZA.

Rheumatoid factor (RF) is primarily an IgM antibody directed against the Fc part of patient's own IgG molecules. RF is usually detected using an agglutination assay with gelatine particles coated with denatured IgG. In presence of RF, macroscopic agglutination is seen within about 1 minute. These antibodies are not specific for RA and occur in a wide range of autoimmune diseases and infections. Antinuclear antibodies (ANA) are autoantibodies directed against cellular proteins or nucleic acids. The most common ANA react with DNA-protein or RNA-protein complexes. These antibodies are generated by a T-cell dependent process driven by the autoantigen.

High titres of ANA (> 1:160) are likely to be significant in assessment of autoimmune disease. The test is usually performed by IIF on fresh frozen sections of rodent liver and/or kidney, or on cultured human cell lines such as HEp-2 cells.

Of the RNA-protein complex targets, anti-Ro antibodies are directed against human antigen and may not be detected on rodent sections. Several immunofluorescence staining patterns occur, reflecting different antigen specificities.

Anti-DNA antibodies – Detection of antibodies to double-stranded DNA (dsDNA) is central to diagnosis of SLE. Antibodies to single-stranded DNA are found in a wide range of autoimmune and infectious conditions. The most specific method for detection of anti-dsDNA antibodies is IIF using the hemoflagellate *Crithidia luciliae,* which has a kinetoplast containing circular dsDNA.

Antibodies to extractable nuclear antigen are useful in severe autoimmune diseases (Table 24).

Table 24: Disease associations of commonly detected antibodies

Autoantibody	*Disease*	*Prevalence*	*Disease specificity*	*Associated clinical features*
• dsDNA	SLE	70%	High	Lupus nephritis
• Sm	SLE	5% (Caucasian) 30–50% (Afro-Caribbean)	High	Vasculitis, CNS lupus
• Ro (SS-A)	SLE	40%	Low	Photosensitivity, subacute cutaneous lupus erythematosus, congenital heart block, neonatal lupus erythematosus
	Sjögren's syndrome	80%	High	Extraglandular disease, vasculitis, lymphoma
• La (SS-B)	SLE	15%	Low	As for Ro
	Sjögren's syndrome	50%	High	As for Ro
• U1 RNP	SLE	30%	Low	Raynaud's phenomenon, swollen fingers, arthritis, myositis (overlap syndrome – mixed connective tissue disease)
• rRNP	SLE	15%	High	CNS lupus (psychosis, depression)
• PCNA (cyclin)	SLE	5%	High	
• Phospholipid	SLE	30%	High	Thrombosis, foetal loss, thrombocytopenia
• Topoisomerase 1	Systemic sclerosis	30%	High	Diffuse cutaneous variant of scleroderma
• Centromere	Systemic	30%	Moderate	Limited cutaneous variant of scleroderma, sclerosis absence of lung disease

Contd…

Contd…

Autoantibody	*Disease*	*Prevalence*	*Disease specificity*	*Associated clinical features*
• RNA	Systemic	20%	High	Diffuse cutaneous variant of scleroderma, polymerases sclerosis visceral involvement
• PM-Scl	Systemic sclerosis	5%	High	Scleroderma/polymyositis overlap
• Jo-1	Polymyositis	30%	High	Polymyositis with fibrosing alveolitis (antisynthetase syndrome)
• SRP	Polymyositis	4%	High	Severe myositis
• Mi-2	Polymyositis	10%	High	Dermatomyositis
• PR3	Vasculitis	90%	High	Wegener's granulomatosis
• MPO	Vasculitis	50%	Moderate	Microscopic polyangiitis, Churg-Strauss syndrome

(SLE: Systemic lupus erythematosus; SRP: Signal recognition particle; PR3: Proteinase 3; MPO: Myeloperoxidase).

Patients with these autoantibodies often have similar clinical features – the tRNA synthetase syndrome (Raynaud's phenomenon, fever, interstitial lung disease, arthralgia and myositis) are located in the cytoplasm and hence not often detected on routine ANA.

Antiphospholipid (anticardiolipin) antibodies (ANCA) are associated with increased risk of vascular thrombosis, recurrent foetal loss, livedo reticularis and thrombocytopenia.

Antineutrophil cytoplasm antibodies (ANCA) – Two main antigenic targets are proteinase 3 (PR3), which is associated with cANCA, and myeloperoxidase (MPO) associated pANCA. The combination of cANCA and PR3 is highly specific for Wegener's granulomatosis, whereas pANCA-MPO occurs in microscopic polyangiitis and Churg-Strauss syndrome but is less specific.

Autoantibodies in monitoring of disease activity – Rising levels of dsDNA antibodies in SLE correlate with increasing disease activity, and an increase PR3 levels occur in Wegener's granulomatosis, however the increased antibody levels can precede clinical relapse by many months.

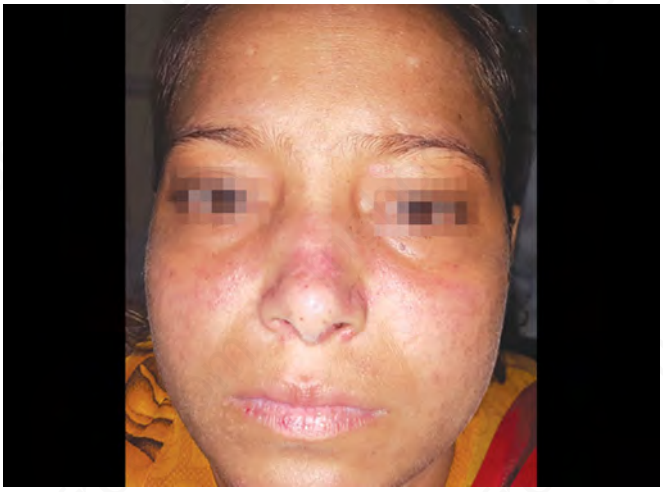


Fig. 37: Malar rash

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with protean clinical manifestations that may affect any organ or system. Table 25 gives classification criterial of SLE.

Table 25: Classification of SLE (American college of Rheumatology)

• Malar rash (Butterfly rash Fig. 37)
• Discoid rash (Fig. 38)
• Photosensitivity
• Oral ulcers
• Non-erosive arthritis
• Pleuritis or pericarditis
• Renal disorder
Persistent proteinuria >0.5 g/day or 3+ if not quantified
Cellular casts
• Neurological disorder
Seizures in absence of known metabolic derangements or offending drugs
Psychosis in absence of metabolic derangements or offending drugs
• Haematological disorders
Hemolytic anemia
Leucopenia
Lymphopenia
Thrombocytopenia
• Immunological disorder
Abnormal anti-DNA titre
Anti-Sm antibody
Antiphospholipid antibodies
• Positive antinuclear antibody
SLE is diagnosed when 4 out of 11 criteria are documented at any time in the history.

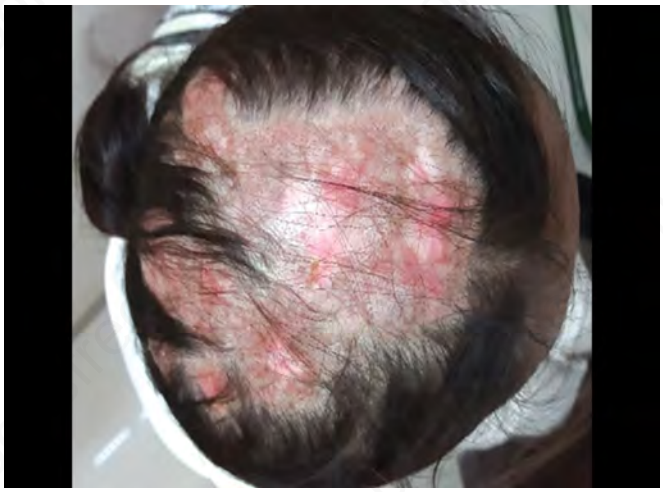


Fig. 38: Discoid lupus

The disease is characterized by flares, remissions and autoantibodies directed against several intracellular and cell-surface antigens.

New diagnostic criteria is introduced which is as given in Table 26.

Table 26: Systemic Lupus International Collaborating Clinic Criteria for Classification of Systemic Lupus Erythematosus

Clinical manifestation	*Immunological manifestation*
Skin	ANA > reference negative value
• Acute, subacute cutaneous LE	Anti-dsDNA
• Chronic cutaneous LE	Anti-Sm
Oral ulcers	Anti-phospholipid
Alopecia	Low serum complement
Synovitis	Positive direct Coombs test
Renal	
Prot/Cr ≥0.5	
RBC casts	
Biopsy	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000) or Lymphopenia (<1000)	
Thrombocytopenia (<100000)	
Renal biopsy read as systemic lupus qualifies for classification as SLE even if none of the other above features are present	
Presence of any 4 criteria (must have at least 1 in each category) qualifies patient to be classified as having SLE	

AETIOLOGY

Genetic factors – Prevalence of SLE in first-degree relatives is ten times that in control groups.

- HLA alleles A1, B8, DR2 and DR3 have shown association with SLE in Caucasian populations
- Deficiencies in classical pathway complement C1q, C_2 and C_4 are strongly associated with development of lupus-like disease
- IgG receptors on mononuclear phagocyte cells clear IgG-containing immune complexes from the circulation, and associations have been found between SLE and presence of low-affinity IgG receptors.

Humoral and environmental influences. SLE and other immune diseases, e.g. Sjogren's syndrome and RA are more common in women.

Drugs such as minocycline, procainamide, hydralazine and penicillamine can also induce a lupus-like syndrome in susceptible individuals. Ultraviolet light can exacerbate cutaneous and systemic disease in SLE.

Defective clearance of apoptotic cells is considered to be a pathogenic mechanism driving the disease process.

Table 27 enumerates the clinical features of SLE.

Table 27: Clinical features of SLE

Non-specific	Fever, fatigue, anorexia, weight loss or lymphadenopathy • CRP usually not raised
Musculo-skeletal	• Arthralgia, symmetrical, flitting and polyarticular • Synovitis and joint effusions (rare) • Non-erosive Jaccoud's arthropathy (Fig. 39) • Muscle pain, sometimes inflammatory myositis • Avascular necrosis (associated with corticosteroid use) • Osteoporosis (from lack of vitamin D from sun avoidance), menstrual cycle dysfunction, corticosteroid use or lack of exercise
Cardio-vascular	• Pericarditis • Conduction abnormalities often due to IHD. Congenital heart block in 1/20 in children born to mothers with anti-Ro or anti-La antibodies • Immune-related myocarditis (rare) • Accelerated atherosclerosis – Incidence of myocardial infarction and carotid artery stenosis in females aged 35–44 years 50 times than in controls. Factors involved – hyperlipidemia, hyperhomocysteinemia, antiphospholipid antibodies and coronary vasculitis

Contd…

Contd…

Pulmonary	• Pleuritic chest pain with or without pleural effusion • Acute pneumonitis (rare but can be fatal) • Chronic interstitial pneumonitis (seldom severe) • Pulmonary hypertension (from vasculitis, thrombosis and pulmonary artery vasoconstriction) • Shrinking lung syndrome (dyspnoea, diaphragmatic weakness, small lung volumes on radiograph)
Gastro-intestinal	• Anorexia, nausea, vomiting • Oral lesions (discoid, erythematous or ulcerative) • Accelerated dental caries, gingivitis and candidiasis if coexisting Sjogren's • Bowel ischemia and infarction with resultant bleeding, perforation or peritonitis • Diarrhoea due to enteric infections
Renal	• Nephritis – WHO classification: – I Normal – IIa Mesangial deposits – IIb Mesangial hypercellularity – III Focal segmental glomerulonephritis – IV Diffuse proliferative glomerulonephritis – V Membranous – VI Advanced sclerotic lupus nephritis
Cutaneous	• Butterfly rash, maculopapular discoid lesions, vasculitic lesions of fingers and toes (Fig. 40) • Alopecia (Fig. 41)

Contd…

	• Subacute cutaneous lupus (variant with anti-Ro antibodies) • Lupus panniculitis (form of lipoatrophy) • Immunoglobulin (IgG or IgM) and component are often deposited at the dermoepidermal junction in both lesional and non-lesional skin (basis of lupus band test)
Neuro-Psychiatric	**CNS** • Aseptic meningitis • Cerebrovascular disease • Demyelinating syndrome • Headache (including migraine, benign intracranial hypertension) • Movement disorder (chorea) • Myelopathy • Seizure disorders • Acute confusional state • Anxiety disorder • Mood disorder • Psychosis
	Peripheral nervous system • Guillain-Barre syndrome • Autonomic disorder • Mononeuropathy, single/multiplex • Myasthenia gravis • Cranial neuropathy • Plexopathy • Polyneuropathy • MRI may show white matter lesions (thought to represent small infarcts)

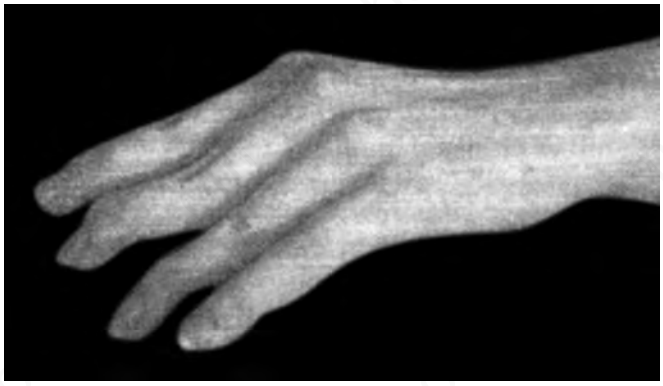


Fig. 39: Jaccoud's arthritis characterized by reducible, non-erosive joint deformities with preservation of hand function. The pathogenesis of this condition is extra-articular and secondary to tendon inflammation and shortening (Swan neck)

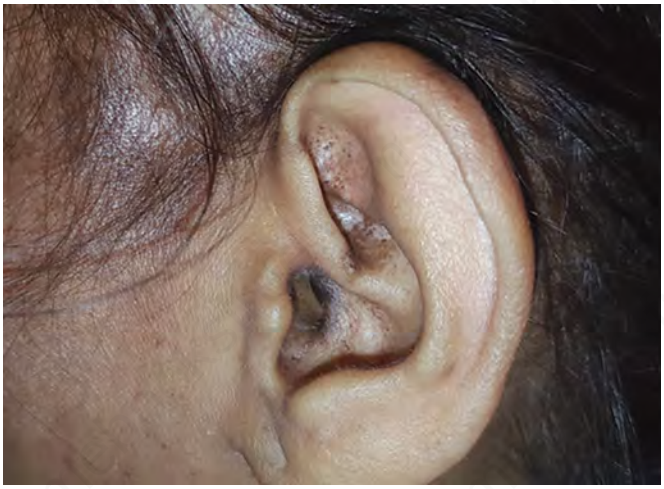


Fig. 40: Pinna rash in SLE

LABORATORY FEATURES

1. *Autoantibodies* are positive in more than 95%. dsDNA is closely related to renal disease and an increase in titre raises possibility of a flare of the disease, particularly if associated with decreasing C3 levels.
2. *Haematological features* – (a) Normochromic, normocytic anemia is present in up to 70%. Lymphopenia and leucopenia are common and thrombocytopenia in about 20%. (b) Lymphadenopathy is common and usually non-tender. (c) Antiphospholipid antibodies and lupus anticoagulant are found in about 30-40%.

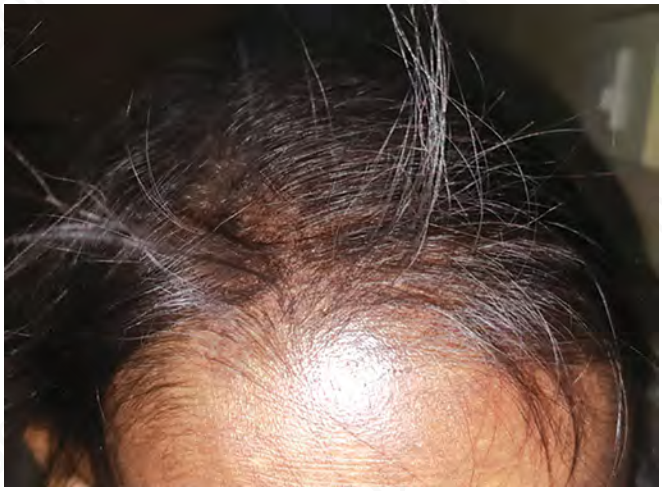


Fig. 41: Alopecia in SLE

Because circulating immune complexes can deposit in tissues and activate component, a decrease in complement factors C3/C4 and increase in their degradation products C3d/C4d are often seen in active disease.

MANAGEMENT

1. **General principles:** (a) Sun avoidance and use of high-factor sun-blocks on sun-exposed areas. (b) Lifestyle modification (exercise, smoking cessation, stress management). (c) Infection risk reduction – e.g. vaccination (modified viral immunizations should not be given to patients taking > 10 mg prednisolone daily or major immunosuppressive drugs).
2. **Drugs**
3. **Other therapies**
   - Methotrexate for serositis and cutaneous and articular manifestations
   - Mycophenolate when standard therapy has failed
   - Dapsone p.o. for vasculitic lesions, cutaneous SLE, oral ulcers and thrombocytopenia

   In patients with renal involvement with proteinuria ACE inhibitors or ARBs are used. As patients are on steroid therapy calcium supplements are needed. SLE is atherogenic condition so patients with deranged lipid profile started on statin therapy.

Disease severity	Drug
Mild	NSAIDs. If control not achieved: Hydroxychloroquine 200–400 mg/d Topical or intralesional corticosteroids can be used for cutaneous lesions
Moderate	Prednisolone < 0.5 mg/kg/d, gradually reduced Azathioprine useful for controlling disease and reducing corticosteroid requirement
Severe	High dose corticosteroids oral or i.v. pulse. Cyclophosphamide i.v. 6 monthly pulses of 1g/m^2 followed by quarterly pulses for 2 years. As per new EULAR guidelines cyclophosphamide can be used at low dosage for induction- 500 mg iv every 15 days for 3 months. Other agents used for induction include mycophenolate mofetil 3 gm/day for 3 months followed by 2 gm/day. Cyclophosphamide and mycophenolate mofetil
	can be used alternative to each other in case of patients not responding to one agent. For those patients who are not responding to both Cyclophosphamide and mycophenolate anti-CD 20 antibody rituximab can be used.

OTHER AUTOIMMUNE DISEASES

BEHCET'S DISEASE

Is characterized by enhanced inflammatory responsiveness and vascular dysfunction, probably caused by infective and immunological insults occurring in genetically predisposed individuals.

Clinical Features

Recurrent oral ulceration similar to aphthous ulcers

Genital ulcers in females affect the vulva and vagina and sometimes the cervix, in males usually on the scrotum, less commonly penis.

Cutaneous: Pustules and acneform lesions. Also erythema nodosum. Transient erythematous rashes, small ulcers and pyoderma granulosum may also occur.

Pathergy is an excessive inflammatory reaction to nonspecific injury. It is demonstrated by appearance of a papule or pustule 24–48 hours after insertion of a 20G needle into the skin of the forearm.

Ocular involvement causes reduction of vision and/or floaters. Anterior uveitis is rapid in onset, may lead to hypopyon formation. Long-term complications include synechiae, cataract, secondary glaucoma and retinal revascularization with sequelae such as vitreous hemorrhage and retinal detachment.

Musculoskeletal – Arthritis in about 40%.

Neurology – Migrainous headaches, cranial nerve palsies, monoparesis and hemiparesis, brain stem and cerebellar symptoms.

Vascular – Superficial and deep vein thrombosis which may involve lower and upper limbs, inferior and superior vena cava, dural sinuses and hepatic and renal veins.

GI ulcers can occur along the large bowel.

Nonspecific manifestations like fatigue and malaise.

Diagnostic Criteria of Behcet's Disease

- Recurrent oral ulceration plus two of the following
- Recurrent genital ulceration
- Eye lesions
- Skin lesions
- Pathergy test

Management

(a) *Cutaneous lesions:* Local corticosteroids applied in an adhesive base, spray or mouthwash. Colchicine to treat mucocutaneous disease that does not respond to local measures. In serious cases, thalidomide (100 mg/d) is effective. (b) *Systemic treatment* – Oral corticosteroids and immunosuppressive agents for significant oral or internal organ involvement. Anticoagulants for deep venous thrombosis.

ANTIPHOSPHOLIPID SYNDROME (APS)

APS is characterized by venous and/or arterial thrombosis and recurrent foetal loss associated with persistent production of antiphospholipid antibodies, a group of autoantibodies directed against cell membrane phospholipids and their associated proteins.

Pathogenesis

It is hypothesized that the interaction of aPL with β2-GPI (and other proteins with antithrombotic function) may lead to thrombosis in both large and small blood vessels.

- There is evidence that anti-β2-GPI antibodies are a marker of thrombogenicity in APS.
- Binding of aPL to β2-GPI is associated with activation of endothelial cells or platelets.
- Binding may also lead to reduced activated protein C activity

Clinical Features

Thrombosis – Deep venous thrombosis in lower limb is the most common manifestation of APS. Occasionally it occurs at unusual sites (e.g. cerebral venous sinuses).

Neurological features – Stroke is the most common and aPL are an important predictor of stroke in men. aPL have also been linked with Sneddon's syndrome (recurrent stroke and livedo reticularis). Dementia and cognitive dysfunction can also occur.

Pregnancy – Persistent aPL are seen in 15% of women with recurrent pregnancy loss. Losses usually occur early (< 12 weeks' gestation). APS may also be associated with placental insufficiency and pre-eclampsia.

Catastrophic APS

Rarely patients present with acute multiorgan failure from extensive microvascular thrombosis.

Other Clinical Complications of APS

Conditions Associated with Production of aPL

- Idiopathic (primary APS)
- Secondary APS – SLE, RA, systemic sclerosis, Behcet's disease, temporal arteritis, Sjogren's syndrome
- Other conditions

  Infections – HIV, varicella, hepatitis C, malaria, syphilis

  Drugs – Phenothiazines, procainamide, phenytoin, quinidine, hydralazine

  Lymphoproliferative disease (lymphoma, paraproteinemia)

Clinical Manifestations in Patients with APS

See Table 28.

Table 28: Clinical manifestations of APS

• Cardiovascular – Venous / arterial thromboembolic disease (Fig. 42), sterile endocarditis with embolism
• Obstetric – Recurrent pregnancy loss, early severe pre-eclampsia
• Neurological – Chorea, dementia, psychiatric disorders, transverse myelopathy, seizure, G-B syndrome
• Haematological – Autoimmune thrombocytopenia, autoimmune hemolytic anemia
• Dermatological – Livedo reticularis, Sneddon's syndrome

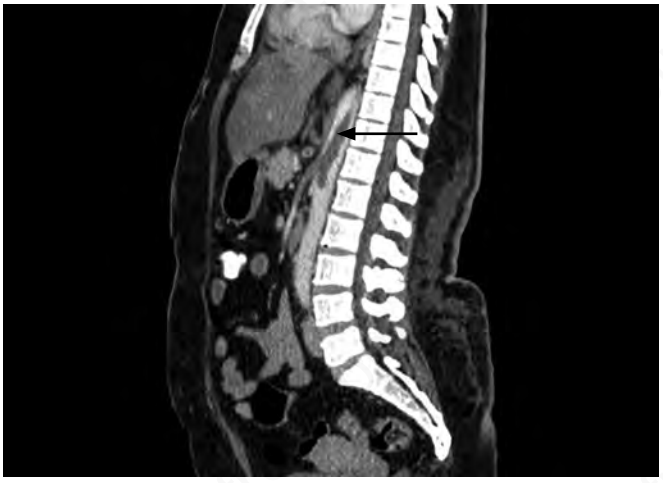


Fig. 42: Aortic thrombus (arrow)

Table 29: Diagnostic criteria of APS.

Clinical criteria
• Vascular thrombosis – One or more episodes of arterial, venous or small vessel thrombosis in any tissue or organ (confirmed by imaging, Doppler studies or histopathology) • Pregnancy morbidity, defined as (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation; (b) one or more premature births of a morphologically normal neonate before the thirty-fourth week of gestation because of eclampsia, severe preeclampsia or placental insufficiency; or (c) three or more unexplained consecutive spontaneous abortions before the tenth week of gestation.
Laboratory criteria
• LA, • Anticardiolipin (aCL) and/or • Anti- β2 GPI antibodies, at intermediate or high titres on two occasions, 12 weeks apart.
APS is considered present when at least one clinical and one laboratory criterion are met.

Diagnosis

Table 29 gives diagnostic criteria of APS.

Indications for Antiphospholipid Antibody Testing

- All patients with apparently spontaneous venous thromboembolism
- Stroke and peripheral arterial occlusive events presenting at <50 years, or older patients with no other risk factors
- Assessment of patients with SLE
- Recurrent pregnancy loss

Management

Initially low molecular weight heparin followed by warfarin; patients who suffer thrombosis while anticoagulated with a target INR of 2.5, are candidates for more intensive anticoagulation with a target of 3.5. For recurrent pregnancy loss – Low dose aspirin as soon as urine pregnancy test becomes positive, and heparin when foetal heart activity is established. It is advisable to continue therapy to term, however in women with a history of late pregnancy complications or thrombosis into the post-partum period. IV immunoglobulin (IVIg) 400 mg/kg every day for 5 days may also prevent abortions, whereas glucocorticoids are ineffective.

SJOGREN'S SYNDROME

Is a chronic inflammatory and lymphoproliferative disease with autoimmune features characterized by progressive mononuclear cell infiltration of exocrine glands, notably the lacrimal and salivary glands (Table 30).

Table 30: Diagnostic criteria for Sjogren's syndrome

Diagnosis on presence of at least of four of the following:
• Ocular symptoms
• Oral symptoms
• Evidence of keratoconjunctivitis sicca (Schirmer's test or Rose Bengal staining)
• Focal sialadenitis by minor salivary gland involvement (lip biopsy)
• Instrumental evidence of salivary gland involvement (parotid sialography or scintigraphy)
• Presence of autoantibodies (anti-Ro or anti-La)
Note: A principal suggested change to these criteria is a positive labial salivary gland biopsy and/or positive Ro/La serology is mandatory for the diagnosis.

- Primary Sjogren's syndrome is defined by xerostomia (dry mouth) and xerophthalmia (dry eyes), often with extraglandular manifestations but without additional autoimmune rheumatic disease.
- Secondary Sjogren's syndrome occurs in association with RA, SLE or another autoimmune rheumatic disease.

PATHOGENESIS – (a) *Genetic factors* – Incidence is greater in relatives of patients with the disorder. (b) *Environmental agents* including herpes viruses, CMV, E-B virus and retroviruses have been known to be a site of latency for various viruses. (c) *Other factors* – such as hormones and abnormalities of apoptosis (programmed cell death) may have a role.

Clinical Features

Glandular Manifestations

(a) Dry, gritty eyes, sensation of burning or foreign body in the eye. (b) Patients may be unable to eat a cracker without drinking fluids ('dry cracker sign'). (c) Dryness of other areas such as nose, throat, vagina, rectum, skin. (d) Swelling of major salivary glands (particularly parotid) is common. (e) Dry mouth – Difficulty with swallowing, speech, taste and wearing dentures. On examination of the mouth, the gloved hand sticks to the mucous membrane. Typical mucosal and glossal signs may include mucosal atrophy and erythema, dorsal papillary atrophy and fissuring of the tongue ('crocodile skin') and chronic candidiasis.

Systemic Manifestations

- Joints – Mainly small joints, symmetrically associated with synovitis

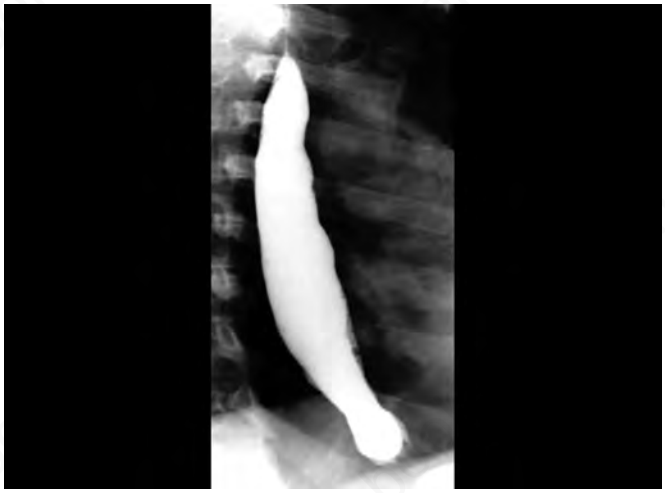


Fig. 43: Dilated oesophagus in systemic sclerosis

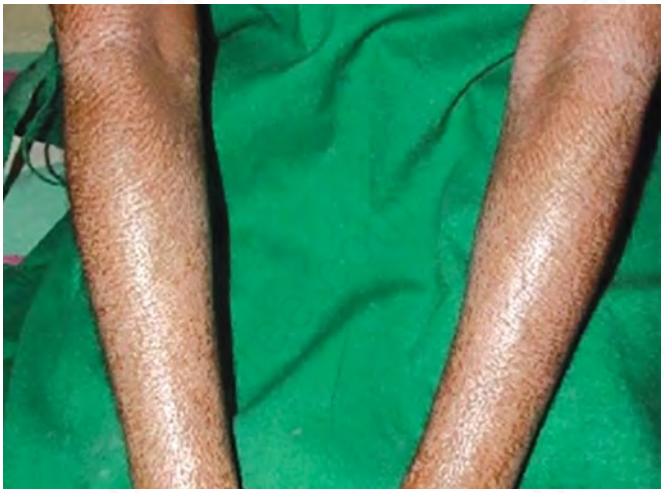


Fig. 44: Salt and pepper skin and systemic sclerosis

- Vasculitis of small and medium-sized vessels causing purpuric rash, skin ulceration, urticaria and neuropathy
- GI – Dysphagia from pharyngeal dryness or oesophageal dysmotility (Fig. 43), chronic atrophic gastritis and subclinical pancreatic insufficiency.
- Pulmonary – Chronic bronchitis, lymphocytic interstitial pneumonitis, pseudo-lymphoma with nodular infiltrates, pleural effusions, pulmonary hypertension and lymphoma.
- Renal – Interstitial lesion causing tubular dysfunction and renal tubular acidosis. This may cause renal calculi, nephrocalcinosis and abnormal renal function.
- Neurological – Peripheral neuropathy, mononeuropathy and autonomic neuropathy.
- Non-Hodgkin's lymphoma occurs in about 5-10% of patients.

Management

(a) *Dry eyes* – Conserving tears with glasses which shield the eye from wind currents and reduce evaporation of tears, and occlusion of the punctum of the lower canaliculus with silicone plugs. Artificial tears. (b) *Dry mouth* – Good oral hygiene, and chewing gums to stimulate residual salivary flow. Treatment of oral candidiasis. Drinking small sips of water. (c) *Drug therapies* – Oral pilocarpine or cevimeline, a derivative of acetylcholine stimulate receptors of salivary and lacrimal gland epithelial cells with improvement of ocular and oral symptoms. Cevimeline is longer lasting than pilocarpine and has fewer adverse effects. Hydroxychloroquine 200 mg b.d. may help arthralgia and myalgia. It may also be effective as immunomodulating agent.

Table 31: Autoimmune diseases with secondary Sjogren's syndrome

RA	Mixed connective tissue disease
SLE	Mixed cryoglobulinemia
Systemic sclerosis	Hashimoto's thyroiditis
Primary biliary cirrhosis	Multiple sclerosis

SYSTEMIC SCLEROSIS

Systemic sclerosis is a homogenous rheumatic disease within the scleroderma spectrum of disorders. These diverse conditions share several clinical features (particularly thickening of the skin resulting from dermal fibrosis and high incidence of episodic peripheral vasospasm – Raynaud's phenomenon) (Table 32). Typical 'salt and pepper' skin may be noticed (Fig. 44).

LOCALIZED SCLERODERMA

Includes linear scleroderma and morphea. Adult-onset morphea may be mild, but some cases are severe and extensive with multiple areas (plaques) of involved skin (generalized morphea).

PATHOGENESIS

Genetic associations are – (a) *Extracellular matrix components* – TIMP1, Fibronectin, and Fibrillin-1. (b) *Cytokines* – CXCR-2, transforming growth factor b3 and b2.

The pathogenesis of systemic sclerosis involves interplay between the immune system, the vasculature and fibroblastic cells.

Pathologic hallmark of SSc is the combination of widespread capillary loss and obliterative microangiopathy together with fibrosis in the skin and internal organs.

Table 32: Spectrum of scleroderma and scleroderma-like disorders

Scleroderma
Localized scleroderma
• Plaque morphea
• Generalized morphea
• Linear scleroderma
• En coup de sabre
• Hemifacial atrophy
Systemic sclerosis
• Diffuse cutaneous systemic sclerosis
• Limited cutaneous systemic sclerosis
• Overlap syndromes
• Systemic sclerosis sine scleroderma
Isolated Raynaud's phenomenon
• Primary
• Secondary
Scleroderma-like disorders
• Eosinophilic fasciitis
• Scleromyxoedema
• Scleredema of Buschke
• Scleroderma diabeticorum

CLINICAL FEATURES

Limited cutaneous systemic sclerosis presents with long history of antecedent Raynaud's phenomenon that is often severe and associated with digital ulceration. Other manifestations are esophageal dysmotility and gastro-esophageal reflux. Skin involvement limited to knees and elbows, and often to wrists and ankles. Other features – Cutaneous telangiectasia (on palms and around mouth), subcutaneous calcinosis and digital infarcts (Fig. 45). The constellation of Raynaud's phenomenon, esophageal involvement and sclerodactyly is termed 'CREST syndrome'.

Diffuse cutaneous systemic sclerosis – often includes tendon friction rub and skin inflammation, but it is the presence of sclerosis proximal to the elbows or knees or affecting the trunk that determines its classification. Affected skin is often intensely pruritic. Symptoms of Raynaud's phenomenon are always present, as also esophageal involvement. Lung fibrosis and hypertensive renal crises are relatively common.

Systemic sclerosis sine scleroderma – Few patients exhibit typical vascular and serological features of systemic sclerosis with visceral combinations such as lung fibrosis, hypertensive crisis or bowel involvement but without any evidence of skin fibrosis.

Limited systemic sclerosis – This group of patients include those who have previously been labelled as having autoimmune Raynaud's phenomenon.

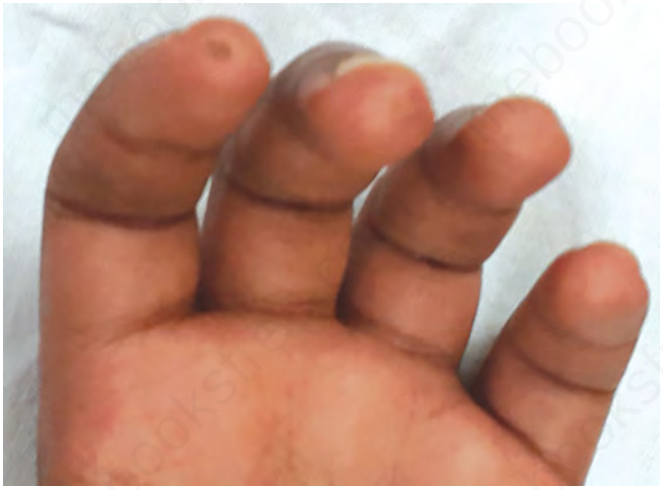


Fig. 45: Digital infarcts

INVESTIGATIONS

Haematology: Anemia, microangiopathic RBC fragmentation (hallmark of renal crisis)

Serum biochemistry: For clues to organ-based complications including myositis, malnutrition and renal impairment.

Acute phase markers: Raised ESR suggests poor prognosis

Autoimmune serology reveals antibody status. Certain internal organ complications appear to occur more often in patients with certain serological reactivities. ANA (seen in all patients of systemic sclerosis), anti-centromere antibody (seen in diffuse systemic sclerosis), anti-topoisomerase I antibody (seen in limited systemic sclerosis).

Organ based: (a) Renal – Monitoring BP, blood, urine. Estimation of GFR. (b) Cardiac – ECG/echo-Doppler, exercise tolerance. (c) Respiratory: Chest radiograph, pulmonary function tests if abnormal CT, bronchoalveolar lavage, biopsy. (d) GI: Barium swallow or radionuclide scintiscan. (e) Other tests according to symptoms – hydrogen breath test, gastroscopy, small and large bowel barium studies.

MANAGEMENT

1. **Disease-modifying therapy**
   a. *Immunosuppressive*: Appropriate for early-stage diffuse cutaneous systemic sclerosis – Cyclophosphamide, antithymocyte globulin and mycophenolate mofetil.

b. *Vascular*: Vasodilatation for Raynaud's phenomenon. Potential for vascular remodelling (e.g. prostacyclin, losartan).
c. *Antifibrotic*: None of proven efficacy. Potential strategies include transforming growth factor β neutralization, prolyl hydroxylase inhibition.

2. **Organ-based treatments**
   a. Gastro-esophageal reflux – Proton pump inhibitors.
   b. Mid-gut disease: Antibiotics
   c. Myositis (often low grade): Prednisolone, methotrexate.
   d. Fibrosing alveolitis: Cyclophosphamide, prednisolone, azathioprine.
   e. Renal insufficiency: Angiotensin converting enzyme inhibitors.
   f. Pulmonary hypertension: Warfarin, prostacyclin analogues, bosentan, ambrisentan.

MYOSITIS

Myositis (inflammation of skeletal muscle) has many causes listed in Table 33.

Table 33: Causes of myositis

• Infectious agents *Viral*: Influenza A and B, hepatitis B, Coxsackie virus, rubella, echovirus, HIV. *Bacterial*: Staphylo., Strepto, Clostridium, M. tuberculosis/M. leprae *Parasitic*: Trichinosis, toxoplasmosis.
• **Drugs and toxins** *Cholesterol-lowering drugs*: Statins, *Drugs for infections*: Rifampicin, sulphonamides, griseofulvin, zidovudine, cytotoxic agents and immunomodulators, hydroxyurea, vincristine, cyclosporine, interleukin-2. *Toxins*: L-tryptophan, alcohol *Others*: Colchicine, D-penicillamine, procainamide, propylthiouracil, carbimazole, growth hormone, tretinoin, corticosteroids.
• **Focal nodular myositis**
• **Eosinophilic myositis**
• **Idiopathic inflammatory myopathies**: Dermatomyositis/polymyositis, inclusion body myositis (Table 34).

Table 34: Classification of idiopathic inflammatory myositis

• Primary idiopathic polymyositis
• Primary idiopathic dermatomyositis
• Dermatomyositis/polymyositis associated with neoplasia
• Childhood dermatomyositis/polymyositis associated with vasculitis
• Polymyositis/dermatomyositis associated with autoimmune disease
• Inclusion body myositis

CLINICAL FEATURES

- **Myositis** – Onset insidious in idiopathic inflammatory myositis. Acute onset dermatomyositis in children and types associated with neoplasia. In inclusion body myositis, patients often have had symptoms for many years at presentation.
- **Muscle weakness** – Proximal muscle weakness most common complaint, causing difficulty in lifting objects overhead, inability to comb or wash hair, and problems with climbing stairs and rising from chairs.
- Digital muscle weakness and atrophy in inclusion body myositis, in which finger flexor weakness and foot drop are common.
- In addition to girdle muscle, other striated muscles including bulbar and intercostal muscles may be weak, leading to hoarseness, dysphonia, difficulty in initiating swallowing, regurgitation of fluids and dyspnoea.
- Muscle pain in 50%.

Cutaneous features – Erythematous or heliotropic rashes affect the eyelids, malar areas, 'V' areas of the anterior chest and upper back. Gottron's papules are erythematous, scaly plaques over knuckles or fingers that often extend onto the forearm (Fig. 46).

See Table 35 for the involvement of other organs with inflammatory myositis.

Table 35: Involvement of other organs with inflammatory myositis

Constitutional	Fatigue, fever, weight loss
Joints	Polyarthralgia and/or polyarthritis
Calcinosis	Intracutaneous, subcutaneous, fascial and intramuscular calcification most common in children, may lead to joint contractures
Lungs	Interstitial alveolitis and fibrosis, aspiration pneumonia, pleurisy and pleural effusion
Heart	Cardiac arrhythmias, myocarditis, pericarditis and rarely cardiac tamponade
GI tract	Pharyngeal dysphagia, dysphonia, ulceration and hemorrhage secondary to vasculitis
Peripheral vasculature	Raynaud's phenomenon, periungual infarction with fissuring of digital pads without ulceration (machinist's hand)
Kidney	Proteinuria, nephrotic syndrome, mesangial proliferative GN, myoglobinuria
Malignancy	Myositis may herald underlying malignancy, notably in men over 40, dermatomyositis is more common than polymyositis

Contd...

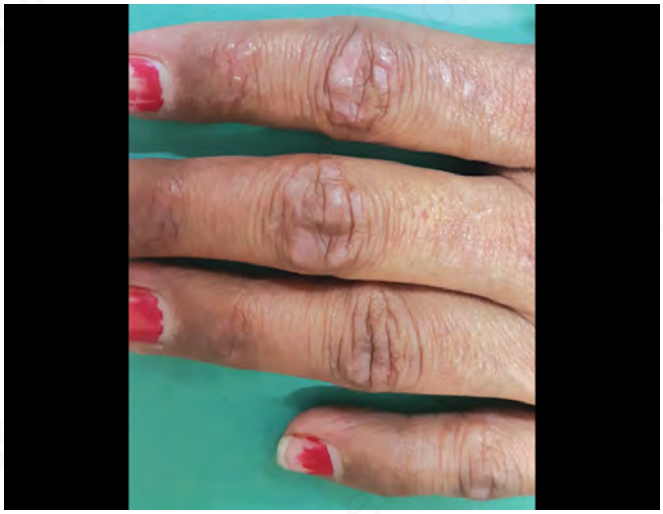


Fig. 46: Gottron's papules

INVESTIGATIONS

General: Raised ESR and CRP. Mild anemia

Muscle enzymes: CPK, aldolase, aspartate and alanine transaminases, and lactate dehydrogenase are enzymes released by damaged muscles. CPK is the most specific enzyme in polymyositis and dermatomyositis, but may be normal or minimally elevated in inclusion body myositis, as also in late stage disease with severe atrophy.

EMG: Typical findings are spontaneous fibrillation potentials, complex repetitive discharges, positive sharp waves at rest and short-duration, low-amplitude complex polyphasic potentials on contraction. Because of the focal nature of myositis, EMG is normal in up to 10% of patients.

Muscle biopsy: Presence of chronic inflammatory cells with muscle necrosis in the perivascular and interstitial areas surrounding myofibrils is pathognomonic. Perivascular inflammation is typical of dermatomyositis, interstitial inflammation of polymyositis. Muscle biopsy in inclusion body myositis shows vacuoles with basophilic granules and both intranuclear and intracytoplasmic tubulofilamentous inclusions.

Serum autoantibodies: ANA are present in more than 80% with polymyositis or dermatomyositis and include Ro (SS-A), U1 (ribonucleoprotein, centromere, mitochondria) and t-RNA synthetase. Other myositis-specific antibodies are antisignal recognition particle (anti-SRP), anti-Mi-2 and anti-PM-Scl.

Other investigations: Chest radiograph, pulmonary function tests, and echocardiography in patients with extramuscular manifestations. MRI of inflamed muscle shows increased signal intensity on T_2-weighted sequences and may help to determine which muscle to biopsy.

DIFFERENTIAL DIAGNOSIS

Neuromuscular disorders that can cause proximal muscle weakness – Spinal muscular atrophies, amyotrophic lateral sclerosis, myasthenia gravis, Eaton-Lambert syndrome, muscular dystrophies. Osteomalacia, adrenal insufficiency, hypophosphatemia, hypothyroidism and carcinomatous neuromyopathy.

MANAGEMENT

(a) *Corticosteroids* – Prednisolone 60 mg/day p.o. initially, dose then tapered. Side effects occur in 40%. (b) *Immunosuppressives* – Azathioprine, methotrexate and cyclosporine in refractory cases. (c) *IV immunoglobulin* in corticosteroid refractory dermatomyositis. Dose 2g/kg monthly given in divided doses over 3 days. (d) *Others* – Plasmapheresis, total body irradiation, thymectomy and extracorporeal photochemotherapy in patients with refractory and severe disease.

Diseases associated with scleroderma-like syndromes

1. *Immunological conditions* – Mixed connective tissue disease, eosinophilic fasciitis, dermatomyositis, SLE, graft versus host disease, acro-osteolysis, lichen sclerosus et atrophicus.
2. *Tumours* – Carcinoid, metastatic bronchial carcinoma, melanoma.
3. *Metabolic diseases* – Porphyria, amyloidosis, Hashimoto's thyroiditis.
4. *Genetic disease* – Phenylketonuria, progeria.
5. *Environmental disease* – Silica-induced and vinyl chloride-induced disease.
6. *Drugs* – Bleomycin, pentazocine.

8. VASCULITIDES

Systemic vasculitides comprise a collection of disorders characterized by presence of fibrinoid necrosis and inflammation of blood vessel walls.

RELATIONSHIP TO AGE

- Kawasaki disease is seen only in children
- Henoch-Schonlein purpura occurs mainly in children, but can present in adults
- Microscopic polyangiitis and Wegener's granulomatosis generally present in adults
- Giant cell arteritis is prominently a disease of the elderly

SMALL VESSEL VASCULITIDES

Primary Small Vessel Vasculitis

Aetiology and pathogenesis: It is an autoimmune disease of unknown aetiology with environmental and genetic factors contributing. It is commonly associated with anti-neutrophil cytoplasm antibodies (ANCA). ANCA correlate closely with clinical activity, activating cytokine-primed neutrophils by binding to antigens expressed on their surface and generating a respiratory burst, releasing proteolytic granules and pro-inflammatory cytokines. ANCA also interfere with the normal processes that resolve inflammation by disrupting apoptotic pathways and preventing apoptotic cell removal that in turn allows progression to secondary necrosis.

Activation of endothelial cells and neutrophils is important for the development of early lesions, but progression is accompanied by influx of monocytes and T cells. This may lead to a sustained cellular inflammatory response with tissue scarring and irreversible damage.

GRANULOMATOSIS WITH POLYANGIITIS (GPA WEGENER'S GRANULOMATOSIS)

***GPA* is** characterized by:

Limited disease

Upper respiratory tract involvement: Sinusitis, otitis media, hoarseness. Complications of granulomatous inflammation can cause mucosal ulceration and nasal septal perforation with a saddle nose. Subglottic stenosis occurs in up to 16% adults and 48% of children. It often becomes fixed and irreversible and can cause life-threatening upper airway obstruction.

On histology, necrotizing vasculitis of small arteries and veins together with granuloma formation, which may be either intravascular or extravascular.

Pulmonary disease: Presentation may be with asymptomatic pulmonary infiltrates or cough, haemoptysis, pleuritis or dyspnoea. Life-threatening alveolar hemorrhage may occur (Fig. 47).

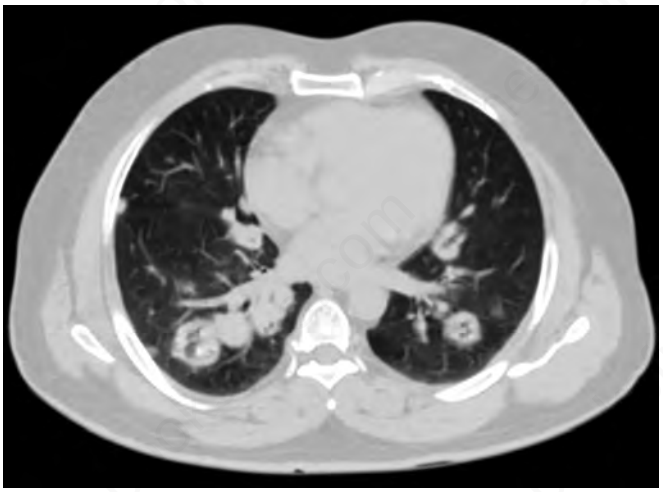


Fig. 47: HRCT lungs showing nudules with cavitations in GPA

Renal disease with glomerulonephritis. The most common abnormality is active urinary sediment with microscopic hematuria.

Other organs – (a) *Ocular involvement* can present as conjunctivitis, scleritis or uveitis. Proptosis may occur and is due to extensive sinus disease. (b) *Myalgia and arthralgia* are common, and non-erosive arthritis can occur. (c) *Skin disease* may manifest as palpable purpura, ulcers and subcutaneous nodules. (d) *Cardiac* – Pericarditis, coronary arteritis. (e) *Nervous system* – Mononeuritis multiplex, peripheral neuropathy. (f) *GI tract* –Haemorrhagic ulceration, bowel perforation.

MICROSCOPIC POLYANGIITIS (MPA)

Microscopic polyangiitis is characterized by necrotizing small vessel vasculitis with no significant immune deposits (pauci-immune) and ANCA directed against the neutrophil protein myeloperoxidase (MPO-ANCA). Systemic symptoms like fever, wt. loss and arthralgia. Renal involvement may range from an active urinary sediment to rapidly progressive glomerulonephritis. So-called idiopathic rapidly progressive GN, without immune deposits and with no systemic features of vasculitis, is now considered part of the spectrum of microscopic polyangiitis.

Haemoptysis and dyspnoea are common. Pulmonary hemorrhage is the main risk factor for death.

EOSINOPHILIC POLYANGIITIS WITH GRANULOMATOSIS (EGPA CHURG-STRAUSS SYNDROME)

EGPA is characterized by hypereosinophilia with tissue infiltration and vasculitis.

Clinical features:

(a) Allergic rhinitis and/or asthma precede development of vasculitis often associated with non-specific symptoms. (b) A rash and mononeuritis multiplex are common presenting features. (c) Pulmonary involvement: Dyspnoea, alveolar hemorrhage or pleurisy and with non-specific pulmonary infiltrates on chest radiography. (d) Cardiac involvement is often a late manifestation and carries poor prognosis. (e) GI: Pain, diarrhoea and ascites. (f) Renal: Involvement is usually mild. (g) Cerebral: Hemorrhage or infarction.

Investigations

Routine laboratory – Generally non-specific. Leucocytosis, thrombocytosis, normochromic normocytic anemia and raised ESR and CRP. Churg-Strauss syndrome is usually associated with blood eosinophilia and elevated IgG levels.

Urinalysis – Urinary sediment with RBC and casts indicates glomerular disease. Proteinuria common. Elevated urea and creatinine levels.

ANCA – Circulating ANCA are an important feature and can be used to monitor disease activity. Wegener's granulomatosis is associated with ANCA directed against proteinase 3, giving agranular cytoplasmic staining pattern on immunofluorescence; the test is very sensitive in patients with active disease, MPO-ANCA are found in microscopic polyangiitis (70%), but PR3-ANCA can also occur. Fifty percent of patients with Churg-Strauss syndrome are positive for MPO-ANCA.

Chest radiography – Pulmonary hemorrhage is seen as diffuse pulmonary shadowing. In Wegener's granulomatosis, pulmonary nodules which often cavitate. Other changes include reticulonodular shadowing, pneumonic changes, collapse and pleural involvement with effusions.

Tissue biopsy – (e.g. skin, lung, kidney) shows three cardinal features – Infiltration by eosinophils, formation of granulomata, necrotizing vasculitis.

Other investigations – Radioisotope-labelled leucocytes scans, CT and MRI for detecting and monitoring involvement of upper respiratory tract and lungs.

HENOCH-SCHONLEIN PURPURA (HSP)

Henoch-Schonlein purpura is a systemic vasculitis characterized by IgA deposition and is most common in children, often below 5 years of age.

Aetiology is unknown, but the condition commonly follows an upper respiratory infection. The disease is characterized by:

- Rash, usually affecting the buttocks and lower limbs
- Arthralgia
- GI involvement with abdominal pain and bloody diarrhoea
- Glomerulonephritis (often more severe with increasing age)
- Other organs, including CNS (seizures) and lung (pulmonary hemorrhage) may be involved.

Diagnosis – Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessels or dermoepidermal junction. (b) Renal histology may vary from mild mesangial proliferation to focal segmental necrotizing GN, but always shows IgA deposition in the mesangium.

Management – Symptomatic treatment. Immunosuppressant in case of renal involvement, particularly with severe disease.

SECONDARY VASCULITIDES

Leucocytoclastic vasculitis (cutaneous or hyper sensitivity vasculitis) is often a part of systemic disease:

- Other vasculitic syndromes – Wegener's granulomatosis, microscopic polyangiitis, Henoch-Schonlein purpura
- Rheumatoid disorders – RA, SLE, dermatomyositis
- Infections – Hepatitis B and C (often from cryoglobulins), HIV, streptococci, IE.
- Paraproteins – Cryoglobulinemia, Waldenstrom's macroglobulinemia
- Others – Inflammatory bowel disease, neoplasia, α_1-antitrypsin deficiency

Investigations – (a) Skin biopsy: Light microscopy, immunofluorescence for IgA. (b) Laboratory tests: FBC, urea and electrolytes, CRP and ESR, antibody screen, hepatitis B and C, cryoglobulins and protein electrophoresis, blood culture.

Management – Symptomatic relief in patients with isolated cutaneous involvement, though immunosuppressants may be required.

Rheumatoid vasculitis presents in patients with severe destructive RA.

Clinical features"

- *Skin*: Purpuric lesions, digital pulp infarcts, livedo reticularis; may be associated with Raynaud's syndrome. Patients with SLE are at increased risk of drug allergies.
- *CNS:* True CNS vasculitis occurs in < 10% of patients. Symptoms range from mild cognitive dysfunction to psychosis, seizures and ischemia. MRI is often unhelpful; it may reveal periventricular white matter lesions but is not diagnostic.
- *CVS:* Extramural arteries may be involved, resulting in myocardial infarction (rare). Myocardial infarction is common as a result of accelerated atherosclerosis.
- Mesenteric vasculitis: With or without infarction, most serious complication. Presents with acute abdomen, fever, vomiting; may have an insidious onset. High mortality. Often associated with renal disease and other internal organ vasculitis.
- Kidney: Focal segmental necrotizing GN with fibrinoid necrosis rare. Distinguished from primary systemic vasculitis by deposition of immunoglobulin and complement.

Investigations – ANA positive in > 95%. Antiphospholipid antibodies and lupus anticoagulants in about 30–40% of patients.

See Table 36 for the management of primary small vessel vasculitis.

Therapies that may prove beneficial include tumour necrosis factor (TNF) blockade, including etanercept (TNF receptor fusion protein) and infliximab (monoclonal chimeric anti-TNF antibody), polyclonal antithymocyte globulin, and other newer immunosuppressant drugs that have shown promise in organ transplantation.

Table 36: Management of primary small vessel vasculitis

Induction therapy	• Continued for 3 months following remission • Prednisolone, 1 mg/kg, maximum dose 80 mg; rapid reduction in corticosteroid dose – 50% over 2 weeks and to a dose of 0.25 mg/kg at week 8 • Cyclophosphamide, 2 mg/kg/day p.o., maximum dose 200 mg; age >60 years reduce by 25%, age >70 years reduce by 50% • Pulsed cyclophosphamide can also be given – 10 pulses over 25 weeks, 15 mg/kg i.v.; dose reductions must be made for age and creatinine • WBC count must be checked between day 10 and 14 following pulse because of decrease in leucocyte count; if <3 x 10°/litre, a suitable dose reduction must be made for the next pulse • There is controversy about the best form of administration for cyclophosphamide; it has been suggested that pulsed cyclophosphamide may be associated with fewer adverse effects but at the expense of a higher relapse rate
Adjuvant therapy	• Life-threatening disease includes creatinine >500 µmol/litre and/or pulmonary **life-threatening disease** haemorrhage • Plasma exchange or methylprednisolone should be considered
Maintenance therapy	• Prednisolone, 5–10 mg/day • Azathioprine, 1.5 mg/kg/day, maximum dose 200 mg • Alternatives to azathioprine include mycophenolate mofetil, 1 g b.d., and methotrexate, 0.15 mg/kg, maximum dose 15 mg once weekly (contraindicated in patients with creatinine >170 µmol/litre) • Consider addition of co-trimoxazole in Wegener's granulomatosis with upper respiratory tract involvement
Limited Wegener's	• Prednisolone and azathioprine or methotrexate
Granulomatosis	• Consider addition of co-trimoxazole
Relapse therapy	• Major relapse – Return to initial induction therapy
	• Minor relapse – Increase corticosteroid dose
Rescue therapy	• Standard induction therapy fails to induce remission in 10% of patients. Patients **relapsing and** who frequently relapse necessitating recurrent use of cyclophosphamide are also a **refractory disease** difficult group

MEDIUM VESSEL VASCULITIDES
POLYARTERITIS NODOSA (PAN)

Aetiology

Some cases are associated with HBV infection. IV drug abuse causes HBV-related disease. It may develop at any age but is most common in men and women aged about 50 years.

Clinical Features

(a) Systemic: Fever, malaise, wt. loss, arthralgia. (b) Orchitis is a characteristic feature. (c) Skin – Nodules and purpura. (d) Peripheral neuropathy. (e) GI: Hemorrhage, perforation, infarction. (f) Cardiac: Angina,

myocardial infarction. (g) Renal: Ischemic nephropathy and renal infarcts leading to severe hypertension and kidney failure. (h) Hepatitis may reflect presence of chronic HBV-associated disease.

Laboratory Findings

- Elevated ESR, CRP. Eosinophilia in 20%
- Abnormalities in tests of organ function, reflecting hepatitis or renal involvement
- HBV test for hepatitis positive
- ANCA test is negative
- Angiography: Microaneurysms or stenotic lesions of medium-sized vessels in the renal, hepatic, splenic or splanchnic circulation.
- Tissue biopsy may be diagnostic, revealing vasculitic lesions.

Deposits of HBsAg, complement and immuno-globulins may be found in the vessel wall in HBV-associated disease.

Management

(a) HBV-associated: Interferon - α or lamivudine, with short-term immunosuppression. (b) Non-HBV: High dose prednisolone 1mg/kg initially tapering over 1 year to 5–10 mg as patient improves. IV cyclophosphamide 0.6 g/m^2 monthly for 1 year also useful.

KAWASAKI DISEASE

Aetiology

Children aged between 6 months and 8 years. Staphylococcal and streptococcal toxins are implicated in the pathogenesis. An infectious agent is suspected. Various toxins are known, including staphylococcal enterotoxins A, B and C1, toxic shock syndrome toxin and streptococcal erythrogenic toxins A, B and C (superantigens). These stimulate a large proportion of T cells in an HLA-DR-dependent, but unrestricted manner, to divide and produce inflammatory cytokines. Some evidence suggests that T cell activation during the acute phase of Kawasaki disease is mediated by super antigen that induces Vb2 expansion.

Clinical Features

Five of the following must be fulfilled:

- Fever of ± 5 days duration (must be present)
- Conjunctival congestion
- Changes in lips and oral cavity – at least one of dry, red, fissured lips, strawberry tongue, reddening of oral and pharyngeal mucosa
- Changes to peripheral extremities – at least one of red palms and soles, indurative oedema, membranous desquamation of finger tips during convalescence
- Macular polymorphous rash on trunk
- Swollen cervical nodes, often unilateral

Cardiac: Most serious consequences are aneurysms, thrombosis and areas of narrowing that may occur in coronary arteries and can be seen on echo-cardiography. The disease can be diagnosed if less than five of the above criteria if coronary aneurysms are present. Myocardial infarction can occur acutely. Myocarditis, acute mitral valve prolapse or pericarditis develop in some.

Non-cardiac – Pyuria, urethritis, aseptic meningitis, tympanitis, arthralgia and arthritis, and abdominal organ involvement (diarrhoea, abdominal pain, obstructive jaundice or cholecystitis).

Investigations – (a) Lab. findings – are nonspecific. Marked thrombocytosis may develop. (b) Cardiac aneurysms can be detected by echocardiography.

Management – IV Immunoglobulin 400 mg/kg/day, and aspirin 100 mg/kg/day for 14 days given within 10 days of onset reduces prevalence of coronary artery aneurysms.

LARGE VESSEL VASCULITIDES

Polymyalgia rheumatica (PMR) is an inflammatory disease seen predominantly in the elderly.

Aetiology: Age and female gender (male:female ratio 1:3) are risk factors for PMR. The acute onset, association with infections and vaccination and occurrence in conjugal pairs suggests an association with an environmental agent.

Clinical features – (a) Diffuse musculoskeletal pain, fever, early morning stiffness in shoulder and pelvic girdles associated with constitutional upset that responds dramatically to corticosteroid therapy. (b) Constitutional symptoms – fatigue, anorexia, wt. loss and low-grade fever. GCA may complicate PMR and PMR may occur before, simultaneously with or after GCA.

Investigations – Elevated ESR and CRP, anemia, mildly elevated alkaline phosphatase and transaminases, reduced serum albumin and raised α2 globulins. Ultrasonography and MRI may show glenohumeral effusion and subacromial bursitis.

Management – Prednisolone 15–20 mg daily reduced to 10 mg daily by 3 months and continued for further 3 months, then reduced by 1 mg/day each month to lowest dose that prevents recurrence of symptoms or increase in CPR/ESR. Addition of azathioprine 1–2 mg/kg/day or

methotrexate 7.5-1.5 mg once a week may facilitate prednisolone reduction.

GIANT CELL ARTERITIS (GCA)

GCA is uncommon before 50 years and about 4 times more common in women.

Clinical features result from combination of inflammation and ischemia in the territory of affected vessels. Extracranial arteries, which have internal and external elastic laminae, are typically involved.

Histopathologically, the disease is a panarteritis with inflammatory mononuclear cell infiltrates within the vessel wall with frequent giant cell formation.

Unilateral throbbing headache usually in temporal area (temporal arteritis) but sometimes occipital (vertebrobasilar arteritis) or diffuse. Pain is severe, can be constant or intermittent and is often associated with scalp tenderness overlying the affected arteries, which may be thickened and nodular with reduced or absent pulsation.

Facial pain and claudication of jaw muscles may occur on chewing or prolonged speaking.

Visual symptoms are caused by occlusion of orbital or ocular arteries and present with partial or complete visual loss in one or both eyes or less commonly diplopia. Visual loss is sudden, painless and usually permanent.

Other neurological symptoms – Vertigo, hearing loss, ataxia due to involvement of vertebrobasilar system.

Involvement of large vessels – Aortic involvement presents with aortic arch syndrome, absent pulses and arm claudication. Thoracic or abdominal aortic aneurysms may be found and can present as acute aortic dissection.

Nonspecific symptoms of inflammatory disease – Fever, malaise, wt. loss. Limb girdle pain and early morning stiffness may occur.

Investigations – Confirmation of diagnosis by demonstration of granulomatous arteritis in a biopsy of the affected artery (usually the temporal artery).

Management – Prednisolone 40–60 mg/day, reduced gradually over 6 months to 10 mg daily. Azathioprine or methotrexate may be added to enable corticosteroid reduction.

TAKAYASU'S ARTERITIS

Takayasu's arteritis presents before age of 40 and is about 10 times more common in women.

Clinical Features

Nonspecific symptoms of inflammatory disease often precede more specific features. Arthralgia and myalgia are common. Some patients develop true arthritis or less commonly, lupus-like rashes, erythema nodosum or glomerulonephritis.

Large vessel disease – 'Aortic arch syndrome' is the term given to disease affecting upper extremities, heart, neck and head. Patients often complain of arm claudication, and radial and brachial pulses are absent (hence formerly called 'pulseless disease'). BP varies by more than 10 mm Hg between the arms and a bruit may be audible over subclavian artery. AR, pulmonary hypertension, angina, CHF, vertigo, syncope, stroke and visual disturbance may occur.

Descending aortic syndrome may cause renovascular hypertension, kidney dysfunction, abdominal pain and acute abdominal bleeding or perforation of a viscus from infarction. Aortic aneurysms may develop and present with acute aortic dissection.

Investigations

Angiography or MRI angiography: Most common lesion is a smooth, concentric arterial or aortic narrowing (Figs. 48 to 52). Less commonly irregular narrowing, complete occlusion and fusiform or saccular aneurysms.

Management

Initially treatment is same as GCA, but the response is slower and often cytotoxic drugs may be required. Surgery or angioplasty may be required but should be deferred until the inflammatory component of the disease has been controlled.

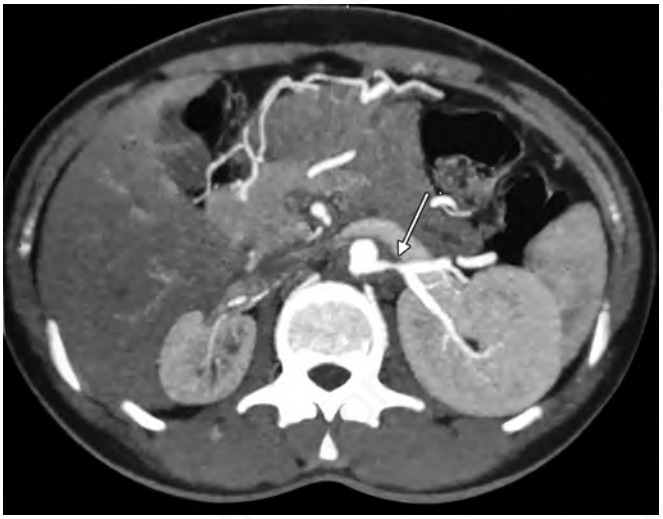


Fig. 48: TA showing right canal artery stenois (arrow)

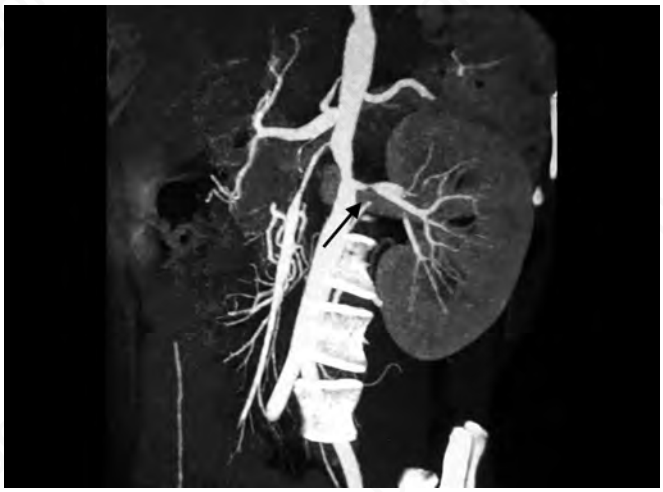


Fig. 49: TA showing stenosis of renal canal artery (arrow)

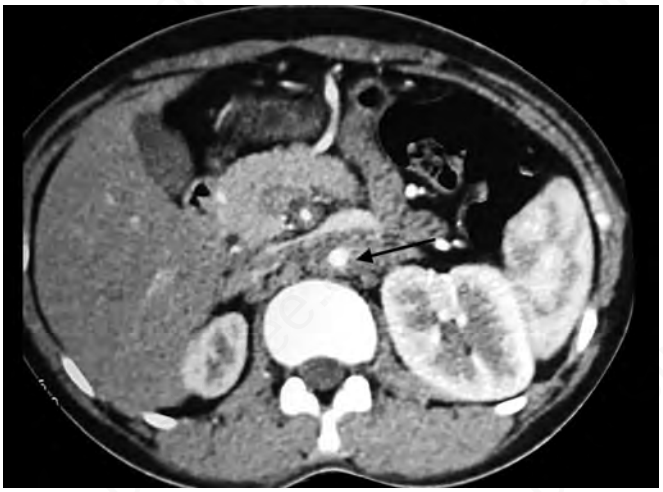


Fig. 50: TA showing in flammed abdominal aorta (arrow)

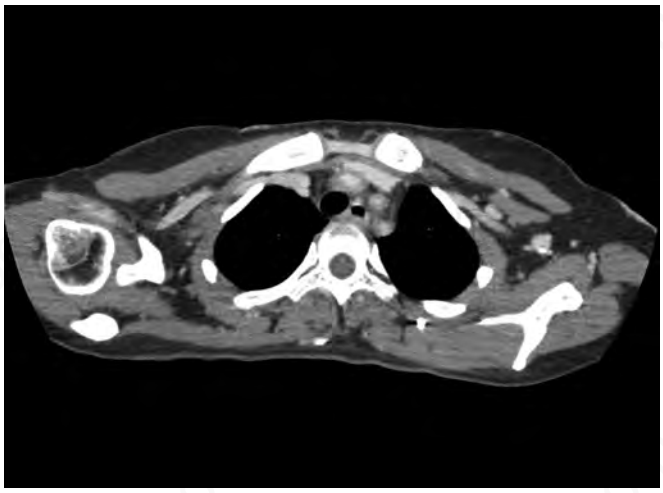


Fig. 51: TA MRI showing inflamed aortic arch and its branches

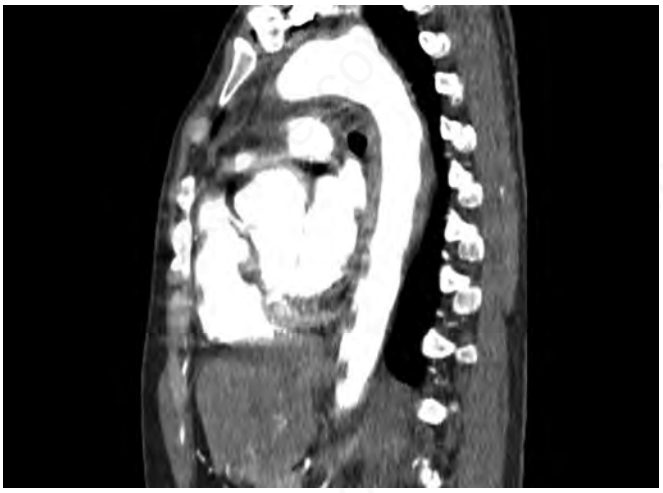


Fig. 52: Thoracic aorta thickening

9. BONE DISORDERS

OSTEOPOROSIS

PRIMARY OSTEOPOROSIS

Osteoporosis is a disease characterized by low body mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent increase in fracture risk. Table 37 gives risk factors for osteoporosis.

Table 37: Risk factors for osteoporosis

Independent of bone mineral density
Age
Previous fragility fracture
Maternal history of hip fracture
Oral glucocorticoid therapy
Current smoking
Alcohol abuse
Rheumatoid arthritis
Body mass index ≤ 19
Falls
Post-transplantation

Contd…

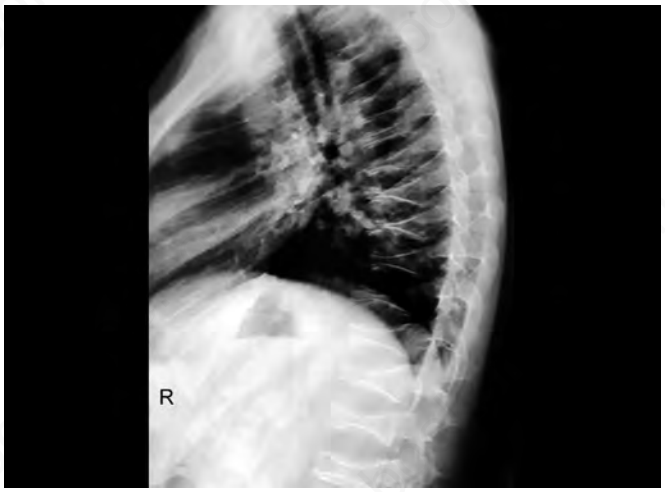


Fig. 53: Osteoporosis of spine Lateral X-ray

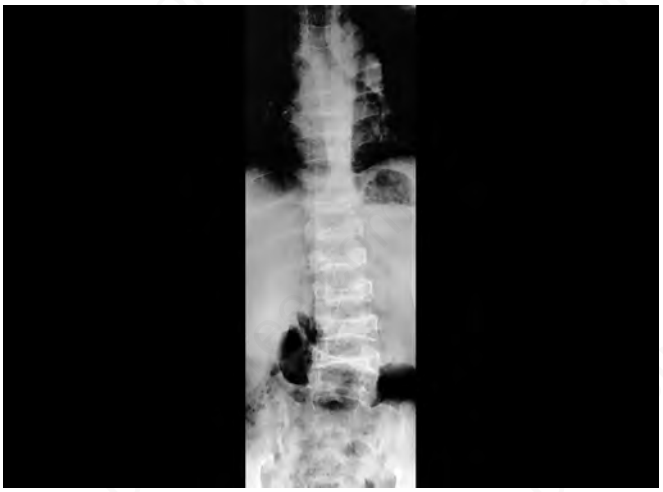


Fig. 54: Osteoporosis spine AP X-ray

Contd…

Depending on bone mineral density
Untreated hypogonadism
Malabsorption
Endocrine disease
Chronic kidney failure
Chronic liver disease
Chronic obstructive pulmonary disease
Immobility
Drugs: Phenytoin, heparin, barbiturates, hypervitaminosis A

Diagnosis

1. **History of fracture.** Fractures associated with osteoporosis are – vertebral fractures (leading to loss of height, kyphosis and back pain), hip fracture, Colles fracture of distal radius.
2. **Radiographs** – of dorsolumbar spine (lateral view) – Prominence of vertical trabeculae, generalised loss of contrast between bone and soft tissue. Also at times vertebral biconcavity or invagination of the disc into the vertebral spongiosa (Schmorl's nodes). Collapse of vertebrae and anterior wedging of vertebral bodies (Figs. 53 and 54) may be asymptomatic.
3. **Bone density measurements:**

Dual energy X-ray absorptiometry (DXA) is the gold standard. The technique uses two X-ray beams that pass almost simultaneously through bone. The difference in attenuation between the two bones gives the bone density in gms/sq cm. The DXA scan is usually performed in the spine, both hips and both wrists.

The bone densities are then plotted against a normal database to give the standard deviation from normal i.e. the T score, which is the bone density of the patient compared to young healthy adults of the same sex.

For post-menopausal women, the T-score values are classified as follows:

1 to 0	Normal
0 to –1	Normal
–1 to –2.5	Osteopenia
< 2.5 (e.g. 3, 4.5)	Osteoporosis

4. **Biochemistry** (*See* Table 38)

Table 38: Markers for bone resorption and bone formation

Bone resorption	*Bone formation*
• Calcium Osteolytic bone metastases • Hydroxyproline • Collagen cross links Urinary Pyridinoline Desoxypyridinoline • Skeletal imaging – Radiographs GI, bone scans and MRI • Tartrate-resistant acid phosphatase	• Serum osteocalcin • Bone specific alkaline phosphatase • Serum assay of IC-terminal procollagen peptide and N-terminal peptide

SECONDARY OSTEOPOROSIS

Table 39 gives causes of secondary osteoporosis.

Table 39: Causes of secondary osteoporosis

1. *Endocrine disorders* Hyperparathyroidism Hypogonadism

Contd…

Contd…

Cushing's syndrome
Hyperthyroidism
Diabetes mellitus
Acromegaly
Prolactinoma
Pregnancy and lactation

2. *Hemopoietic disorders*
Plasma cell dysplasia
Multiple myeloma
Macroglobulinemia
Systemic mastocytosis
Leukemias and lymphomas
Sickle cell disease and thalassemia minor
Gaucher's disease

3. *Connective tissue disorders*
Osteogenesis imperfecta
Ehlers Danlos syndrome
Marfan's syndrome
Homocystinuria
Menkes' disease
Scurvy

4. *Drug-induced*
Glucocorticoids
Heparin
Anticonvulsants
Methotrexate
Cyclosporine
Aluminium containing antacids

Contd…

Contd…

5. *Immobilization*

6. *Renal disease*
Chronic kidney failure
Renal tubular acidosis

7. *Nutritional and GI disorders*
Malabsorption
Total parenteral nutrition
Gastrectomy
Hepatobiliary disease
Chronic hypophosphatemia

8. *Others*
Familial dysautonomia
Reflex sympathetic dystrophy

Management

Calcium – 1.5–2 g/day. If calcium malabsorption or associated osteomalacia; cholecalciferol 0.25 mg (10,000 IU) or Alfacalcidol 0.5 µg/day or Calcitriol 0.25 µg/day or Calcitonin 200 IU/day intranasally, alternate nostrils daily. (b) *Oestrogen therapy* – for small thin women, early menopause or oophorectomy, parous women, strong family history of osteoporosis, and those with prolonged amenorrhoea or oligomenorrhoea. Dose – Conjugated equine oestrogen 0.625 mg daily or its equivalent.

Drugs used in osteoporosis are listed in Table 40.

Table 40: Pharmacological therapy

Bisphosphonates

Drug	Dosage	Route of administration	Indications
Alendronate	70 mg once weekly or 5 or 10 mg o.d.	Oral	Postmenopausal Glucocorticoid-induced
Etidronate	400 mg/day x 2 wks every 3 months	Oral	Postmenopausal Glucocorticoid-induced
Ibandronate	150 mg once monthly 3 mg once every 3 months	Oral IV	Postmenopausal Postmenopausal
Risedronate	35 mg once wkly or 5 mg o.d.	Oral	Postmenopausal Glucocorticoid-induced
Raloxifene	60 mg o.d.	Oral	Postmenopausal
Strontium ranelate	2 g o.d.	Oral	Postmenopausal
Teriparatide	20 µg o.d.	S.C. inj.	Postmenopausal
Parathyroid hormone	100 µg o.d.	S.C. inj.	Postmenopausal

Note: Oral bisphosphonates must be taken fasting with a full glass of water, and the individual must stay sitting or standing without food or drink for next 30–60 minutes.
Strontium ranelate is alternative front line option to alendronate or risedronate, particularly in people for whom these drugs are contraindicated or not tolerated.

Calcitonin – also inhibits bone resorption and has been shown to prevent menopausal bone loss. Given by sc injection. Side effects of nausea and facial flushing. (i) *Sodium fluoride* – stimulates osteoblasts and new bone formation. Dose 40-60 mg/day. Side effects include GI symptoms and pain in lower limbs due to stress-fractures.

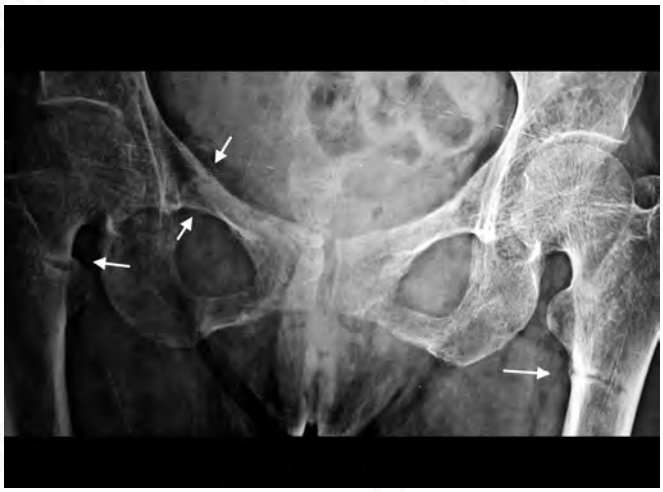


Fig. 55: Looser's zones (arrows)

Table 41: Causes of osteomalacia/rickets

Cause	*Mechanism*
• Vitamin D deficiency	*Defective intake/formation* Lack of solar exposure (D_3) and of dietary intake or fat malabsorption (D_2) Severe chronic liver disease *Increased/wasteful metabolism* Liver-enzyme-inducing drugs e.g. phenytoin, phenobarbitone, carbamazepine, rifampicin *Failure of activation, 25 (OH) D1-25 $(OH)_2$ D* Chronic renal failure Hereditary vitamin-D dependent rickets type I *Target organ defect* Hereditary vitamin-D dependent rickets type II
• Phosphate deficiency	*Poor intake* Aluminium hydroxide excess binding of dietary phosphate *Increased loss* X-linked hypophosphatemia (vitamin D-resistant rickets) Fanconi's syndrome Renal tubular acidosis Ureterocolic anastomosis Tumour-associated
• Chronic metabolic acidosis Osteoblast / mineralization defect	*Renal tubular acidosis* *Ureterocolic anastomosis* *Hypophosphatasia* Etidronate therapy Aluminium intoxication (in renal disease)
Cause	*Mechanism*
• Drug-induced osteomalacia	High doses of sodium fluoride or of first generation bisphosphonates (e.g. etidronate). Anticonvulsants in patients with marginal vitamin D supply.

OSTEOMALACIA

It is a disorder of mineralization of the adult skeleton. See Table 41 for the causes of osteomalacia.

CLINICAL FEATURES

Bone pain and tenderness, deformity, proximal muscle weakness, waddling gait. Tetany.

DIAGNOSIS

1. *Biochemistry* – (a) Plasma calcium low or normal. (b) Serum phosphate raised. (c) Raised alkaline phosphatase.
2. *Radiography* – Looser's zones, linear areas of defective mineralization especially in long bones, pelvis and ribs (Fig. 55).
3. *Therapeutic trial* – Response to vitamin D or one of its active metabolites.

TREATMENT

Depends on the cause. e.g. bicarbonate and potassium supplements in renal tubular acidosis, phosphate supplements in hypophosphataemic syndromes. Vitamin D or one of its potent derivatives alfacalcidol or calcitriol. Cholecalciferol can be administered as chewing tablets or oro spray. Vitamin D_3 orally as tablets or capsules.

Oncogenic osteomalacia is a rare tumour associated disorder characterized by hypophosphatemia, phosphaturia, normocalcemia, and oesteomalacia in absence of nutritional or drug history suggestive of vitamin D deficiency or generalized renal tubular acidosis. Patients typically present with bone pain or proximal muscle weakness. Tumors associated with this disorder are generally benign, the commonest being hemangiopericytoma.

OSTEOPETROSIS

Osteopetrosis or marble bone disease is a heterogenous group of disorders characterized by a generalized increase in bone density caused by defective osteoclastic bone resorption.

CLINICAL DISORDERS

1. *Osteosclerosis* – (a) Osteopetrosis with delayed manifestations (Albers-Schonberg disease). A benign form

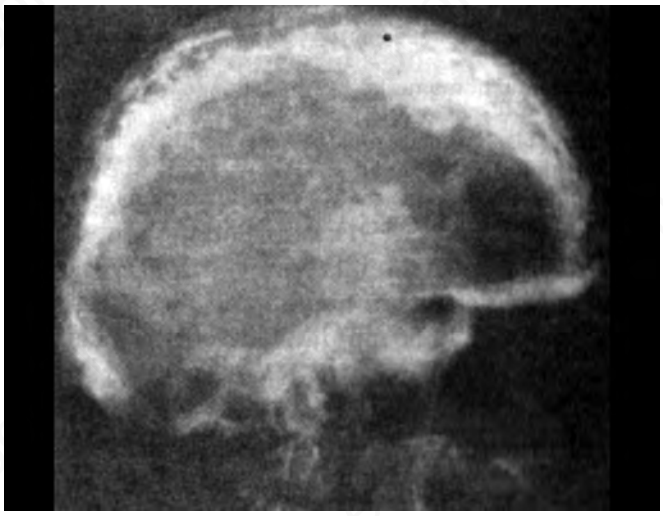


Fig. 56: Radiograph of the skull of patient with advanced Paget's disease showing thickening, disordered new bone formation (cotton-wool patches), and basilar impression

of osteopetrosis. May be asymptomatic. Occasionally facial palsy or deafness from cranial nerve compression. (b) Osteopetrosis with precocious manifestations – Presents in infancy with failure to thrive, abnormal bleeding and anemia. (c) Pyknodysostosis – Short stature, enlarged skull, short and broad hands and feet and blue sclerae.

2. *Craniotubular dysplasia* – Abnormal skeletal modelling with little bone sclerosis.
3. *Craniotubular hyperostosis* – Overgrowth of bone, with resultant alteration of contour and increased skeletal density.

PAGET'S DISEASE OF BONE

A bone disease characterized by excessive osteoclastic bone resorption, associated with a compensatory, but disorganized increase in bone formation. Precise aetiology unknown, but the finding of inclusion bodies in the osteoclasts nuclei suggests a possible viral infection (measles or respiratory syncitial virus).

CLINICAL FEATURES

(a) Bone pain – Localised pain in affected bones, nocturnal pain common. Thickening and deformity and bowing of bones. Local warmth and tenderness from increased vascularity. (b) Osteoarthritis due to limb shortening. (c) Kyphosis due to vertebral collapse. (d) Neurological symptoms – Involvement of spine may lead to paraparesis. Entrapment neuropathies of cranial and peripheral nerves. (e) Skull changes –Enlargement of skull vault, prominent scalp veins, platybasia due to skull base softening, cranial nerve compression and deafness due to distortion of auditory meatus or ossicles, or nerve compression. (f) Fundoscopy – Angioid streaks.

Complications – (a) High cardiac output due to increased blood flow. (b) Pathological fracture. (c) Sarcoma. (d) Urinary stone formation.

INVESTIGATIONS

1. *Radiology and scintigraphy* – (a) Early lytic lesions in long bones seen as flame-shaped resorption front, or in skull as osteoporosis circumscripta (Fig. 56).

   (b) In mixed phase, bone may expand with loss of cortical and medullary differentiation. Patchy involvement of skeleton is best demonstrated by bone scintigraphy. (TC^{99} MDP bone scan).
2. *Biochemistry* – (a) Alkaline phosphatase is a marker for bone formation. (b) Hydroxyproline is a marker of osteoclastic bone resorption.
3. *Histology* – Early lesion is replacement of normal bone by abnormally large osteoclasts. As the disease progresses sclerosis becomes more prominent.

MANAGEMENT

Indications for treatment – (a) Bone pains. (b) Osteolytic lesions in weight-bearing bones. (c) Neurological complications. (d) Delay or non-union of fractures. (e) Before and after major orthopaedic surgery. (f) Immobilization hypercalcaemia. *Drugs* – Bisphosphonates suppress or reduce bone resorption by osteoclasts – (a) Etidronate 400 mg daily for 3-6 months is effective and well tolerated, but should be avoided in patients with pseudofractures and deformities of weight bearing joints as it may cause osteomalacia. (b) Pamidronate for severe Paget's disease. Initial therapy with 2–3 60 mg infusions, followed by 60 mg at 3-month intervals. (c) Tiludronate 400 mg daily p.o. for 3–6 months is more potent than etidronate with no adverse effect on mineralization. May induce negative focal bone balance giving rise to radiological translucencies. May be repeated if necessary at interval of 6-12 months.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI, brittle bone disease) is a disorder of bone matrix. It is AD inherited disorder and the clinical heterogeneity is largely the result of the great number of different molecular defects within the genes that encode pro-a_1 and pro-a_2 type I collagen.

Cl. Fs. – The clinical hallmark of OI is osteopenia with recurrent fracture and skeletal deformity, defective formation of dentin (dentinogenesis imperfecta) (Fig. 57).

Type I: Sclerae with bluish discolouration that is particularly apparent during childhood, relatively mild osteopenia with infrequent fractures and deafness (30% incidence). Increased numbers of cortical osteocytes may be detected by bone biopsy.

Type II: It is often fatal within first few days or weeks of life because of respiratory complications. Affected new-borns are often premature and small for gestational age, and have short, bowed limbs, numerous fractures, a markedly small skull and a small thorax.

Type III: Progressive skeletal deformity due to recurrent fractures, and short stature that partly results from fragmentation of growth plates.

Type IV: Sclerae are normal colour, but skeletal deformity, dentinogenesis imperfecta and hearing loss are typical findings.

Radiological features – Severely affected patients show generalized osteopenia, shaping defects of long bones and deformity as a result of recurrent fractures. Platybasia is common and can progress to basilar impression.

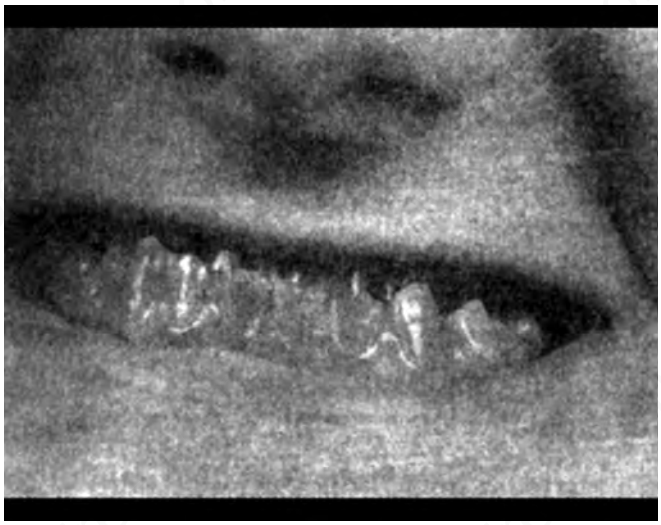


Fig. 57: Dentinogenesis imperfecta

Tr. – Antiresorptive therapy with iv Pamidronate in children before 3 years. Oral bisphosphonates may be effective in older children and adults. Supportive treatment.

OTHER SCLEROSING BONE DISORDERS

Albers-Schonberg disease (autosomal dominant osteopetrosis type II) – Generalized osteosclerosis with thickening of vertebral end-plates (sandwich vertebrae) and bone within bone in the pelvis.

Pyknodysostosis – AR disorders with short stature, large cranium, small facies and skeletal fragility.

Progressive diaphyseal dysplasia – Patchy thickening of bone associated with pain, gait abnormalities and muscle wasting.

10. MISCELLANEOUS

Syndrome of remitting seronegative symmetrical synovitis with pitting oedema

RS_3PE syndrome is used to describe patients who have peripheral seronegative, symmetrical polyarthritis with tenosynovitis, and pitting oedema present mainly over the dorsum of hands, especially in men above the age of 60. The course is benign and there is good response to corticosteroids.

Table 42: Rheumatological disease associated with malignancy

• Dermatomyositis	• Carcinoma (lung, oesophagus)
• Scleroderma	• Adenocarcinoma (lung, kidney)
• Primary Sjogren's syndrome	• Lymphoma Lymphoma and myeloma
• Rheumatoid arthritis	Lymphoma and lung cancer
• Systemic lupus erythematosus	

Table 43: Rheumatological manifestations of malignancy

• Metastatic bone disease
• Myopathy
• Pancoast tumour
• Coccydynia
• Hypertrophic pulmonary osteoarthropathy
• Fibromyalgia/polymyalgia
• Gout
• Arthritis

Table 44: Differential diagnosis of arthritis and oedema of the hands

Disease	*Clinical features*	*Investigations*
RS_3PE syndrome	Aged male. Symmetrical polysynovitis. Dramatic response to low dose corticosteroids. Long term remission after withdrawal. Good prognosis	Negative RF and ANF. Absent bony erosion on X-ray
Mixed connective tissue disease (Sharp syndrome)	Young female. Raynaud's phenomenon +	High titre ANF (speckled) with anti-native ribonucleoprotein.
CPPD crystal arthropathy (chondrocalcinosis)	Predominantly elderly female. Absence of constitutional symptoms. Asymmetric oedema. Responsive to NSAIDs	Chondrocalcinosis on hands, knee, pelvis on X-ray. CPPD (calcium pyrophosphate dihydrate) crystal demonstration by polarised light analysis of synovial fluid
Reflex sympathetic dystrophy	Exquisitely painful oedema (often bilateral), vasomotor and skin alterations. True arthritis absent, predisposing factors +	Absent markers of systemic inflammation. Radiology (X-ray, bone scintigram and MRI) helpful
Amyloid arthropathy	Rare disease, firm pseudo-oedema. Frequent carpal tunnel syndrome, nodules +; slow and insidious onset without morning stiffness. Multiple visceral involvements. No response to corticosteroids	Proteinuria, monoclonal gammopathy or light chain in urine (AL type). Free amyloid debris in synovial fluid; specific birefringence with Congo Red staining on biopsies
Reiter's or psoriatic spondyloarthropathy	Axial, skin, ophthalmic or genitourinary signs and symptoms. Mostly asymmetrical. Occasionally firm and non-pitting lymphoedema	HLA-B27 +; sacroiliitis +
Late onset spondyloarthropathy	Middle aged men. Asymmetrical pitting oedema of lower limbs with oligoarthritis. Constitutional symptoms ++; poor response to corticosteroids	HLA-B27 +; Absent axial disease
Rheumatoid arthritis	Female predominance, symmetrical synovitis of MCPs and IPs. Good (not dramatic) response to corticosteroids. Unilateral pitting oedema, associated . with rupture of neighbourhood joint.	RF +, bony erosions on radiography
Polymyalgia rheumatica	Elderly patient with female predominance. True peripheral synovitis rare; usually mild. Dramatic response to corticosteroids. Long-drawn treatment with frequent flares	Temporal artery biopsy

CHAPTER 10

Infectious Diseases and Infections

1. DIPHTHERIA

Diphtheria is caused by superficial infection of respiratory tract or skin with toxin-producing strains of Corynebacterium diphtheria. The organisms do not actively invade deep tissue or blood, but multiply locally producing diphtheria toxin. This results in necrosis of mucosal cells and production of a thick, grey pseudomembrane. Diffusion of toxin into circulation causes neurological and myocardial complications.

Incubation period – 2 to 6 days.

CLINICAL TYPES

1. RESPIRATORY GROUP – includes majority.

   Nasal diphtheria – Unilateral or bilateral nasal discharge, at first serous and often blood stained; later thick, mucopurulent and foul smelling.

   Faucial diphtheria – The pseudomembrane adheres to the fauces, and attempts to remove it leaves a raw, bleeding surface. Cervical lymph nodes enlarge and there is oedema of the neck, which may be severe and progress to 'bull-neck'.

   Laryngeal diphtheria – More common in infants. Membrane involves larynx and also spreads to trachea and bronchi. Initial symptoms are hoarseness, brassy cough and noisy breathing. Progressive laryngeal obstruction produces inspiratory stridor. Lower intercostal spaces are sucked in as not enough air flows in to fill the lungs. If not relieved child dies of hypoxia.

2. NON-RESPIRATORY GROUP – include vulva, vagina, umbilical cord, conjunctiva, auditory meatus, tongue and oesophagus. Glans or coronal sulcus of penis after circumcision in infants. Cutaneous diphtheria may present as a chronic ulcer or a persistent shallow ulcer with punched out areas.

Diagnosis – Throat or laryngeal swab for culture on blood tellurite agar. Suspicious colonies are identified by a black or grey appearance on this medium.

Complications – Aspiration of membrane can cause respiratory obstruction.

1. **Cardiovascular** – Myocarditis with circulatory failure, cardiac arrhythmias such as heart block, cardiac failure.
2. **Neurological** – Palatal palsy, paralysis of accommodation with difficulty in reading small print, polyneuritis with weakness of muscles of extremities.

DIFFERENTIAL DIAGNOSIS

Faucial Diphtheria

1. *Acute follicular tonsillitis* – It is the most important differential diagnosis of faucial diphtheria (Table 1).
2. *Moniliasis* – Most common in infants, patches of soft deposit of fungus on buccal mucosa and tonsils. Exudate white and characteristically arranged as small linear membranes. Monilia albicans will be seen on smear.

Table 1: Differences between faucial diphtheria and follicular tonsillitis

Diphtheria	*Follicular tonsillitis*
History of epidemic, or of exposure	History of previous attacks
Insidious onset	Acute onset
Tough, ashy-grey uniform deposit	Soft, yellowish white deposits in spots or patches with intervening areas of redness
Membrane very adherent, bleeding points when torn off	Membrane easily removed leaving smooth surface
Pillars of fauces and uvula may be involved	Deposit limited to tonsils
Fever usually slight	Fever high
Cervical glandular enlargement rare	Cervical glands commonly enlarged

3. *Vincent's angina* – Gingivitis with ulceration, no toxaemia, marked foetor of breath, presence of fusiform bacillus and spirillum.
4. *Infectious mononucleosis* – occurs usually in older children. Exudate as a rule remains white. Glands in neck enlarge but remain discrete. Patient usually less ill.
5. *Agranulocytosis* – Gingivitis with ulcerating membranous lesions of tonsils, palate, or gums. Fever and malaise. Diagnostic blood picture.
6. *Acute leukaemia* – Haemorrhages, enlargement of spleen, liver and lymph glands.
7. *Post-tonsillectomy slough* – No tendency for lesions to spread.
8. *Quinsy* – Usually unilateral, glands enlarged and tender.
9. *Mumps* – may simulate periadenitis of diphtheria but swelling in mumps fills up posteriorly the depression between angle of jaw and mastoid process. Orifices of Stensen's ducts injected, no membrane, no toxaemia.
10. *Secondary syphilis* – Glairy deposit on tonsils. Hoarseness due to laryngitis.
11. *Leukoplakic patches* – Seen mainly in men over 40 years of age. White patches also on gums, cheeks or dorsum of tongue.
12. *Scarlet fever* – Tonsillopharyngitis may be membranous or ulceromembranous. Typical rash.

Laryngeal Diphtheria

1. *Acute catarrhal laryngitis* – Few constitutional symptoms, catarrh dominant, slight obstructive signs, usually no paroxysms.
2. *Measles* – Catarrhal symptoms. Koplik's spots, no membrane; later rash.
3. *Acute bronchiolitis* – Affects children mainly under 2 years of age. Initial non-specific upper respiratory infection symptoms followed by cough, reluctance to feed and rapid wheezing respirations. Short inspiratory gasps may be accompanied by widespread crepitations.
4. *Staphylococcal pneumonia* – Onset with upper respiratory symptoms with rapid deterioration, dyspnoea, pallor and grunting respirations. Signs of localized consolidation.
5. *Asthma in first attack* – Usual age 9 months onwards. Expiratory distress, no stridor. Rhonchi with expiratory spasm.
6. *Laryngismus stridulus* – Sudden onset, recurrent nocturnal attacks of dyspnoea, no membrane, few general symptoms. Rickets or other evidence of tetany.
7. *Congenital laryngeal stridor* – Starts in first week, lasts up to two years. Obstructive signs but no dyspnoea; symptoms constant but less at night; sometimes abnormalities of jaw and chest.
8. *Papilloma of larynx* – Gradual onset, chronic cough and alteration of voice, slowly progressive dyspnoea with occasional paroxysms, stridulous breathing chiefly inspiratory; direct laryngoscopy shows tumour.
9. *Acute oedema of glottis* – Abrupt onset, persistent dyspnoea, history of nephritis or angio-oedema, etc. Oedema on laryngoscopy.
10. *Foreign body in larynx* – Acute onset with violent paroxysms of coughing; dyspnoea persistent, may abate after onset to return later; stridulous breathing chiefly inspiratory. Foreign body seen on laryngoscopy or X-ray.

Table 2: Type of diphtheria and dose of diphtheria antitoxin

Type of diphtheria	*DAT*
Nasal	10,000
Tonsillar (unilateral)	10,000
Tonsillar (bilateral)	40,000
Confined to tonsillar fossa	20,000
Membrane extending beyond tonsillar fossa:	
On one side of pharynx wall	30,000
To anterior pillar and palate	40,000
To palate on both sides	60,000
Laryngeal (pulse additional dose as above) for membrane on the throat	30,000
Bullneck diphtheria	1,20,000
Cutaneous	10,000
Prophylactic dose for contacts	6,000

MANAGEMENT OF DIPHTHERIA

1. General care – (a) Complete rest in bed for 2 weeks, or longer if necessary. (b) Diet – Fluids in acute phase; soft or semisolid diet in early convalescence. (c) Glucose – IV to counteract hypoglycemia associated with toxaemia. (d) Relief of sore throat or headache with gargles and codeine.
2. Diphtheria antitoxin – DAT should be given as early as possible by IV drip or IM injection or half IV and half IM as a single dose. Dose for children and adults is same (Table 2).

   Assessment of DAT dose – Evidence that growth of the membrane has been checked within 24 hours, no newly formed membrane and the existing membrane should be more opaque. If new membrane has formed, dose of DAT should be repeated.

3. ANTIBIOTICS – Erythromycin 250 mg by mouth every 6 hours for 5–7 days to terminate production of new toxin and for preventing secondary infection.

   Procaine penicillin G, 600000 U IM q12 h (for children: 12, 500–25000 U/kg IM q12h) until the patient can swallow comfortably; then oral penicillin V, 125–250 mg qid to complete a 14-day course.

   Eradication of C. diphtheriae should be documented after antimicrobial therapy is complete. A repeat throat culture 2 weeks later is recommended. For patients in whom the organism is not eradicated after a 14-day course of erythromycin or penicillin, an additional 10-day course followed by repeat culture is recommended.

4. MANAGEMENT OF LARYNGEAL DIPHTHERIA – In addition to general and specific measures, relief of obstruction to breathing by steam inhalations (the bed being covered with a mosquito net) alternating with O_2 inhalations a antispasmodics such as salbutamol. If restlessness persists and respiration remains distressed, tracheostomy should be performed. The air must still be kept moist. The tube can be removed after about a week. Assisted respiration may be necessary.

5. MANAGEMENT OF COMPLICATIONS

   (a) *Respiratory and cardiac complications* can be minimized by monitoring including regular ECG and early intervention (e.g. pacing for conduction disturbances, drugs for arrhythmias). Tracheostomy or intubation may be necessary to ensure continued patency of potentially compromised airway, and mechanical removal of any tracheobronchial membrane.

   (b) *Paralysis* – (i) Of palate – Thickened feeds to prevent regurgitation. (ii) Of pharynx – Raise foot of bed for drainage of mucus. Digital swabbing or mechanical aspiration. Tube feeding may be necessary or IV. (iii) Respiratory paralysis – Use of ventilator and maintenance of adequate airway. (iv) Peripheral palsies – Rest, splinting and physiotherapy.

IMMUNIZATION – *For active immunization,* see Chapter 12.

For passive immunity – Prophylactic dose for contacts 6000 units DAT, for babies 4000 units. Immunity lasts for about 2 weeks. May be given simultaneously with active immunization.

SCHICK TEST – to detect immunity to diphtheria.

Method – One arm is injected intradermally with 0.1 mL of diphtheria toxin, and the other arm with a control injection of 0.1 mL diluted diphtheria toxin.

Results – (a) Sensitivity is indicated by an area of induration or redness more than 12 mm in diameter, occurring within 24–28 hours at the site of control injection. (b) Lack of immunity (positive reaction) is indicated by redness, with or without induration, at the site of toxin injection, and no or less reaction at control site. (c) Immunity (negative reaction) is indicated by a reaction at the site of toxin injection which is less than or equal to that at the control site.

2. MENINGITIS

Meningitis is inflammation of the leptomeninges caused by infectious agents; however infiltration of the meninges by leukaemic or other malignant cells also produces inflammatory meningitis. For bacterial meningitis, peak age of incidence is less than 5 years. Neonates, particularly premature are at particular risk.

PATHOGENESIS

Pathogens usually gain access to the meninges through the blood stream. Most of the organisms causing bacterial meningitis are commonly carried in the upper respiratory tract, and there is evidence that invasion is triggered or facilitated by a coincident infection with a second pathogen (e.g. influenza virus) causing mucosal damage or an immunosuppressive effect. Table 3 lists the causes of meningitis.

ASEPTIC MENINGITIS

- Viral – e.g. HSV 2, polio.
- Partially treated pyogenic meningitis.
- Non-infective causes – (i) Vasculitis (esp. SLE). (ii) Meningeal carcinomatosis. (iii) Sarcoidosis. (iv) Behcet's/Whipple's disease. Vogt-Koyanagi syndrome.
- Specific infections in which causative agent may not be identified on ordinary microscopy or culture – TB or cryptococcal meningitis, neurosyphilis, leptospirosis, brucellosis.
- Parameningeal suppuration.

BACTERIAL MENINGITIS

Epidemiology and bacteriology – Introduction of H. influenzae and Neisseria meningitidis vaccines has reduced the incidence of meningitis from these organisms. Risk of bacterial meningitis may be increased in other conditions.

Defects in the three pathways of complement activation are associated with increased susceptibility to meningococcal infection, including terminal complement components, the properdin system and mannose-binding protein. Splenic dysfunction (as in sickle cell disease) is associated with increased risk of pneumococcal

Table 3: Causes of meningitis

Infectious causes	
Bacterial	**Viral**
Common	Mumps
N. meningitidis	Echovirus
S. pneumoniae	Coxsackievirus types A and B
H. influenzae	Genital herpes simplex virus types 1 and 2
Neonatal	
Group B Strepto.	Other herpes viruses
E. coli	Epstein-Barr virus
L. monocytogenes	Varicella-Zoster virus
Uncommon	Cytomegalovirus
Staph. aureus	HIV
Ps. aeruginosa	Lymphocytic choriomeningitis virus
B.burgodoferi	
Rare	Adenovirus types 3 and 7
Salmonella	Arboviruses
Shigella	
N. gonorrhoea	
Mycobacterial	**Protozoal**
M. tuberculosis	Naegleria
Fungal	**Spirochaetal**
Cryptococcus	Leptospirosis
neoformans	Syphilis
Candida	Lyme disease
	Ricketssial
	Typhus fever
Non-infectious causes	
Malignant	
Leukemic meningitis	
Other non-infectious causes	
Sarcoidosis	
Connective tissue disease	
SLE	
RA	
Sjögren's syn.	
Vasculitis	
Granulomatous polyangiitis	
Eosinophilic granulomatous polyangiitis	
CNS vasculitis	

meningitis, and T lymphocyte defects (congenital or caused by chemotherapy, AIDS or malignancy), result in increased risk of Listeria monocytogenes meningitis. Streptococcus pneumoniae is the most common pathogen in cases secondary to a breach or defect in the mucocutaneous barrier such as basal skull fracture, midline facial defects or inner ear fistulas. Penetrating cranial trauma and CSF shunt increase risk of meningitis caused by staphylococci (particularly coagulase-negative species) and other skin pathogens.

Pathophysiology

- Transmission, colonization and invasion of nasopharyngeal epithelium.
- Survival in the blood stream by evading host immune response.
- Meningeal invasion. Bacteraemia may be rapidly followed by seeding of meningeal pathogens and secondary infection of the meninges.
- CSF inflammatory response.
- Cerebral oedema and thrombosis. Cerebral oedema may be caused by reduced CSF reabsorption by the arachnoid villi, or by vasogenic or cytotoxic means. Bacterial meningitis causes loss of cerebrovascular anticoagulation.

Clinical Features

Relate to three causes

1. *Infection* – Fever, rigors, toxaemia.
2. *Increased intracranial pressure* – Headache, nausea, vomiting, deterioration of consciousness, hypertension, bradycardia.
3. *Meningeal irritation and inflammation* – Neck rigidity, positive Kernig's sign, photophobia.

Other presenting features include

- Cranial nerve palsies most commonly IIIrd, IVth, VIth and VIIth
- Focal neurological deficits such as nystagmus, aphasia, ataxia and peripheral nerve palsies
- Partial or generalized seizures – tend to be more common in Strep. pneumoniae and HIV meningitis
- Purpura or petechiae in meningococcal meningitis, with or without features of septic shock (Waterhouse-Friderichsen syndrome)
- Less specific presentation may be seen in young infants and in elderly such as lethargy, poor appetite, listlessness, diarrhoea and vomiting

Diagnosis

Examination of CSF (refer investigations in Neurology).
Typical CSF findings in acute bacterial meningitis:

- Raised WBC count (usually 100–60,000 cells/mL predominantly neutrophils)
- Reduced CSF glucose (30–40% serum glucose level)
- Raised CSF protein (0.5–5 g/litre)
- Increased opening pressure (>180 mm H_2O)

Gram-staining of CSF is positive in over 90% of cases of haematologically acquired meningitis.

Blood culture – should be performed in all patients with suspected meningitis, and latex agglutination bacterial antigen test or polymerase chain reaction analysis (to detect bacterial DNA) may be performed on blood or CSF to try to obtain a diagnosis. Such tests remain positive for several days after administration of antibiotics. Laboratory markers of poor prognosis include low peripheral WBC count, thrombocytopenia, absence of CSF pleocytosis and high CSF protein levels.

Viral meningitis – Genexpert (Xpert EV) has high degree of accuracy of enteroviral meningitis.

CT – Normal CT does not exclude raised intracranial pressure in bacterial meningitis, but can be used to exclude significant space occupying lesions, which would contraindicate lumbar puncture. When a clinical diagnosis of meningococcal meningitis is made on presence of a purpuric or petechial rash, LP should not be performed. Such patients are commonly in compensated septic shock, and the procedure may worsen their cardiovascular and respiratory status.

Differential Diagnosis of Meningitis

A. ***Meningism*** – Neck stiffness in presence of normal CSF. May be seen occasionally usually at onset, in typhoid fever, apical pneumonia, acute exanthema, acute pyogenic tonsillitis, pyelonephritis, cervical lymphadenopathy (Table 4).

B. ***Other infections of CNS***

1. *Poliomyelitis* (in the early 'meningeal phase') – usually of short duration, meningeal signs not marked, hyperaesthesiae common, paralysis common and more extensive. Lumbar puncture at once differentiates.
2. *Viral meningoencephalitis* – Distinct CSF findings – Glucose level normal, proteins less elevated (typically 0.5–2 g/L), and lymphocytosis.
3. *Post-infectious meningoencephalitis* – Rare sequel of measles or influenza, or less frequently chickenpox, mumps or rubella, and certain vaccines.
4. *Focal infections* – such as brain abscess and subdural empyema may have similar clinical features. Investigations to determine a specific aetiology include CSF examination with specific stains for mycobacteria and fungi, cytology, antigen detection, serology, viral culture and blood culture. CT or MRI of brain.
5. *Non-infectious illnesses* – though uncommon may cause CNS inflammation including malignancy, collagen vascular syndromes and exposure to toxins. CSF findings are useful.

Table 4: Difference between meningitis and meningism

Meningitis	*Meningism*
Slow onset usually	Rapid onset
Neck pain common	No neck pain
Delirium, convulsions or coma common	Delirium, convulsions and coma rare
Vomiting at onset and also subsequently	Vomiting at onset only
Pulse and respiration may be irregular; relative bradycardia	No irregularity of pulse rhythm, no bradycardia
Kernig's sign present	Kernig's sign usually absent
Cranial nerve palsies common	Cranial nerves rarely affected
CSF shows definite changes	Increased pressure of CSF with moderate reduction in protein and chloride content

Management

ICU – for patients with severely depressed consciousness, signs of raised intracranial pressure, shock or convulsions.
Antibiotics – Antibiotic coverage for meningitis is given in Table 5.
Corticosteroids– Dexamethasone 0.4 mg/kg b.d for 4 days with the first dose of antibiotic.
Prevention – Primary prevention of bacterial meningitis may be achieved by immunization and by prevention of secondary cases of meningococcal and H. influenzae disease using chemoprophylaxis.

Vaccines – The introduction of conjugate vaccine has dramatically reduced the incidence of this pathogen as a cause of bacterial meningitis, and a pentavalent meningococcal conjugate vaccine or a quadrivalent meningococcal polysaccharide vaccine is advisable at 2, 3 and 4 months of age. Pneumococcal vaccine is poorly immunogenic in children under 2 years of age. It is used in older children and adults at high risk of invasive pneumococcal disease, such as those with reduced splenic function including sickle cell disease, the elderly, diabetics and patients with other chronic diseases.

Table 5: Empirical antibiotic coverage for meningitis

Age group	*Most likely pathogens*	*Antibiotic daily dose*
Neonates	B group streptococci,	Ampicillin (100–150 mg/d)
	E. coli,	+ Cefotaxime (50 mg/kg) or
	Listeria	Ceftriaxone (500–1000 mg/kg/d)
1–3 months	N. meningitides,	Ampicillin
	Strep. pneumoniae,	+ Broad spectrum cephalosporin
	Listeria	(Vancomycin 40 mg/kg)
Older infants, children and adults	H. influenzae,	Ceftriaxone or Cefotaxime
	N. meningitides,	+ Vancomycin
	S. pneumoniae	
Elderly or immunocompromised	S. pneumoniae,	Ampicillin + Ceftriaxone
	Listeria bacilli,	or Ceftazidime + Vancomycin
	L. monocytogenes,	
	Gram -ve bacilli	
Age	*Organisms covered*	*Antibiotics*
16–50 years	S. pneumoniae,	Vancomycin 1 gm q8h (in children 60 mg/kg/d)
	N. meningitides,	+ Ceftriaxone 100 mg/kg/d
	H. influenzae	
>50 years	S. pneumoniae,	Vancomycin 1 gm q8h
	L. monocytogenes,	+ Ceftriaxone 2 gm bd
	Anaerobic gram -ve bacilli	+ Ampicillin 3 gm tds or qds
Post-surgical or post-head injury	Staph. Aureus,	Ceftazidime 2 g q8h
	S. pneumoniae,	+ Vancomycin 1 gm q8h
	Anaerobic gram -ve bacilli	
Organism	*Antibiotic*	
	First choice	*Second choice*
E. coli	Cefotaxime 8–12 g/d	Aztreonam
		or Fluoroquinolone
		or Meropenem
P. aeruginosa	Ceftazidime 6–12 g/d	Aztreonam
	or Cefixime	or Meropenem
Pseudomonas	Ceftazidime 6–12 g/d	Carbenicillin 18–30 g/d
		or Ticarcillin 12–20 g/d
		or Piperacillin 12–18 g/d

3. VIRAL INFECTIONS

INFLUENZA AND RESPIRATORY SYNCYTIAL VIRUS

About 30–50% of acute lower respiratory tract infections are viral in origin; of these influenza and respiratory syncytial virus (RSV) are associated with maximum disease burden.

Influenza

Influenza viruses are small RNA-containing enveloped viruses. There are three types – A, B and C. Influenza A viruses are further classified according to the properties of their surface proteins, haemagglutinin (HA) and neuraminidase (NA) found on the surfaces of influenza viruses. There are 16 known HA subtypes and 9 known NA subtypes which can combine to create novel combinations of influenza. The typical seasonal influenza viruses exhibit frequent point mutations that lead to gradual shifts in their genomes. This process is known as antigenic drift, and it is the reason that new influenza vaccines must be prepared each year. Poultry are the natural reservoirs of type A viruses. Influenza B viruses are only found in humans and

have caused epidemics in the past, but never pandemics. Influenza C virus causes only mild illness in adults.

Incubation period – 1 to 3 days.

Clinical Features

Clinical features of influenza A and B illness.

Onset – Sudden with fever, chilly sensations, and prostration, catarrhal symptoms, headache, pains and dry cough. Sometimes erythematous rash.

Clinical Types

1. *Febrile type* – Only constitutional symptoms – fever, malaise, headache, severe bodyache, catarrh, congestion of eyes and throat, rapid prostration. Dry cough with few or no signs in chest. Fever lasts for 4 to 6 days, there may be relative bradycardia.
2. *Respiratory type* – (a) Bronchitis and bronchopneumonia. (b) Pleurisy, empyema not uncommon. (c) Pneumonia – (i) Fulminating rapidly fatal form in which pneumonia is present from the onset. (ii) Progressive form in which on the 2nd or 4th day signs of pneumonia begin to develop with copious fine crepitations usually basal. The sputum may be pinkish, frothy and copious, or tenacious mucus of several hues. (iii) Late form in which often after apparent recovery from the primary influenza, pneumonia suddenly supervenes on the 4th to 10th day after the onset.
3. *GI type* – Temperature rarely above 37.5°C, severe anorexia and vomiting, abdominal discomfort and general prostration. Tympanitis, diarrhoea and continued fever may simulate typhoid fever.
4. *Malignant type* – Severe toxaemia, cyanosis and rapid cardiac failure. Always fatal.
5. *Nervous type* – Headache sometimes very severe, delirium, intense depression which may continue after the acute illness. A true meningitis may occur.

Diagnosis

The Genexpert system can perform rapid and accurate determination of Flu A and Flu B infection along with identification of the H1N1 novel influenza virus strain. The assay results are obtained in 2 hours which is important in starting appropriate therapy and maximizing infection control measures.

Complications and Sequelae

Table 6 gives population groups with high risk of getting influenza complication.

Table 6: Population group with high risk of influenza complication

1. All children from birth to <5 years old, especially <2 years
2. All persons ≥50 years old
3. Pregnant women
4. Adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic or metabolic disorders (including diabetes mellitus)
5. Persons who have immunosuppression (including that caused by medications or by HIV infection)
6. Children and adolescents (6 months to 18 years old) who are receiving long term aspirin therapy and who might be at risk for Reye's syndrome after influenza virus infection
7. Residents of nursing homes and other long-term care facilities
8. Persons who are morbidly obese (body mass index >40 kg/m^2)

1. *Respiratory* – Bacterial bronchopneumonia or lobar pneumonia, less often pure viral pneumonia. These may be concurrent with initial viral infection or follow after an interval. Staphylococcal pneumonia is a serious sequel and may be fatal, less severe infections may result in lung abscess.
2. *Nervous system* – Post-influenzal psychoses, insomnia, irritability, polyneuritis, neurasthenia, meningitis and haemorrhagic encephalitis.
3. *Circulatory system* – Cardiac dilatation, irregularities, pericarditis, endocarditis.
4. *Suppuration* – Otitis media, mastoiditis, sinusitis.
5. *Miscellaneous* – Thrombophlebitis, arthritis, orchitis, myositis, nephritis, intestinal hemorrhage.

Management

1. *Analgesics and sedatives.*
2. *Cough suppressive such as codeine.*
3. *Antibiotics* for secondary infections such as otitis media and pneumonia.
4. *Antiviral drug* – Neuraminidase inhibitors – act on viral neuraminidase, and prevent release of virus particles from infected cells and can be given po or by inhalation (see later).

Prevention – (a) *Vaccines* – Haemophilus influenzae type B conjugate vaccine 1 mL subcut; or 0.1–0.2 mL intradermally given 1–2 weeks apart gives moderate temporary protection against current strains. (b) *Anti-viral agents* – Ribavirin 100–200 mg is effective as vaccination against Influenza A strains and may be started at the same time as vaccination to provide protection until immunity develops.

AVIAN INFLUENZA

Since over last 10 years, there have been regular outbreaks of avian influenza, with H5N1 virus being detected in poultry.

***Avian influenza subtypes*:** Avian influenzae virus are subtypes of type A influenza viruses, and there are multiple varieties of avian influenza. These can be divided into low pathogenic (H5, H7 or H9) and high pathogenic forms (H5 and H7). Infection by low pathogenic viruses may be asymptomatic and/or cause minor symptoms such as decreased egg production and ruffled feathers. Low pathogenic forms can cause disease in humans. H7 infections infrequently cause conjunctivitis and/or upper respiratory symptoms. However, infection by high pathogenic viruses may infect multiple internal organs.

***Virulence of avian influenza*:** Possible mutations in the H5N1 virus raise the possibility of a human pandemic. As with all influenza viruses, there have been numerous changes in the H5N1 genome.

***Transmission of avian influenza in humans*:** The main route of transmission of influenza virus is via inhalation of infected respiratory droplets from coughing and sneezing. Because humans are rarely exposed to avian influenza virus, there is minimum immunity to these particular viruses.

Symptoms vary from the typical 'flu' symptoms of fever, sore throat, cough and muscle ache, to much more severe symptoms including eye infections, pneumonia, acute respiratory distress and potentially fatal complications such as multiorgan failure. Majority of morbidity and mortality has been in healthy children and young adults as compared to seasonal influenza viruses which produce more severe symptoms in the elderly and immunocompromised.

***Diagnosis*:** (a) A laboratory test termed. Influenza A/H5 (Asian lineage) virus Real-time RT-PCR Prime and Probe set can provide preliminary results on suspected H5 influenza samples within 4 hours of testing. (b) Isolation of virus.

***Treatment*:** Two drugs Zanamivir and Oseltamivir are neuraminidase inhibitors which block the action of neuraminidase which normally breaks the bonds attaching new influenza viruses to the exterior of an infected cell. The viral particles cannot detach from the infected cell thus limiting the extent of the infection.

Oseltamivir can be used in individuals over 1 year of age who have symptoms for less than 2 days. *Dosage:* Adults – 75 mg bd orally for 7 days and in children dose according to body weight. To be started within 2 days of onset of symptoms. Common side effects are nausea and vomiting.

Zanamivir is approved for treatment of uncomplicated influenza virus infection in patients over the age of 7 years who have symptoms for less than 2 days. *Dose:* Two inhalations bd for 5 days. It is not recommended for chronic respiratory diseases such as asthma or COPD, because it can cause breathing problems. It may also cause headache and diarrhoea.

Vaccine. Influenza vaccine (human live attenuated) Pandemic (H1N1).

Respiratory syncytial virus – RSV is non-segmented enveloped RNA virus. It is best known as a cause of bronchiolitis in infants, but can cause respiratory tract infection in all age groups.

Transmission – is primarily through large aerosol droplets or secretions. This leads to widespread nosocomial infection.

Clinical features – Severity of RSV infection is related to age. In young infants early signs may include difficulty in feeding, nasal congestion, cough and otitis media compatible with URTI. Fever is often present.

Abnormal breath sounds, tachypnoea and hypoxemia suggest lower respiratory tract involvement. Bronchiolitis and pneumonia are the two primary manifestations of progression to LRTI; they may be difficult to distinguish and can occur simultaneously. Clinical features of bronchiolitis are wheezing and hyperaeration.

Older children and adults with RSV infection have a milder respiratory infection with a lower likelihood of LRTI. Disease in the elderly may be particularly severe, up to 50% develop pneumonia.

Investigations – (a) *Chest radiography* findings are nonspecific, and commonly include hyperaeration and peribronchial thickening, with areas of consolidation and interstitial infiltrates in patients with pneumonia. (b) *Laboratory diagnosis* depends on detection of viral antigen in respiratory secretions by immunofluorescence, rapid antigen tests or culture of the virus.

Management – Supportive care – Maintenance of oxygenation, nutrition and hydration. Ventilatory support in severe cases. Bronchodilators may be beneficial. Antiviral like ribavirin is used for those who are immunocompromised or severely ill.

No benefit has been found in the treatment of HRSV pneumonia with standard immunoglobulin; immunoglobulin with high titers of antibody to HRSV (RSVlg), which is no longer available; or chimeric mouse-human monoclonal IgG antibody to HRSV (palivizumab).

- Prophylaxis in infants <2 years receiving O_2 therapy for bronchopulmonary dysplasia
- Infants born <32 weeks with bronchopulmonary dysplasia are likely to benefit from 6–12 months prophylaxis

- Should not be used in cyanotic congenital heart disease
- Initiate treatment before RSV season
- Defer live virus vaccine (e.g. MMR) until after last dose.

H1N1 INFLUENZA

H1N1 virus Influenza results from one of the three basic types of influenza virus namely A, B or C, which are classified within the family Orthomyxoviridae. These are structurally and biologically single-stranded RNA viruses which vary antigenically. A distinctive feature of influenza viruses is that mutations occur frequently and unpredictably in the eight gene segments and especially in the haemagglutinin gene. The emergence of an inherently virulent virus during the course of a pandemic can never be ruled out.

H1N1 influenza (also called swine flu, hog flu and pig flu) caused by swine influenza virus (SIV), that usually infects pigs and is endemic in pigs.

Significant surface proteins of the virus include haemagglutinin and neuraminidase based on which the viruses are typed. These proteins determine the immunogenicity.

Transmission – Infection occurs after transfer of respiratory secretions from an infected individual to an immunologically susceptible individual. If the virus is not neutralised by secretory antibodies, it invades airways and respiratory tract cells. Once it enters the host cells, it leads to cellular dysfunction and degeneration, along with viral replication and release of viral progeny.

Communicability of the virus – A patient is infectious to others from 1 day before to 7 days after onset of symptoms. If infection persists for more than 7 days, chances of communicability may persist till resolution of illness. Children are likely to spread the virus for longer period.

Clinical features – After an incubation period of 18–72 hours, systemic symptoms ensue. Abrupt onset with varying degrees of fever. Sore throat may be severe, may be associated with rhinitis. Myalgias range from mild to severe. Ocular symptoms may develop and include photophobia, burning sensation and/or pain on motion. Weakness and severe fatigue may prevent patients from normal activities. Cough and other respiratory symptoms may be initially minimal but progress as the infection evolves. Cough may be unproductive and associated with pleuritic chest pain, and dyspnoea.

Complications – (a) *Pulmonary:* Primary viral pneumonia, secondary bacterial pneumonia and exacerbation of COPD and bronchial asthma. (b) *Extrapulmonary:* Myositis, rhabdomyolysis, myoglobinuria, myocarditis and pericarditis. At times CNS complications may occur including encephalitis, transverse myelitis and GB syndrome and Rae syndrome.

Laboratory findings – Leucopenia and relative lymphopenia are typical findings, there may be thrombocytopenia.

Specimens for viral studies viz. RTP CR and viral culture should be stored at 4°C before and during transportation within 48 hours.

Case Definitions of H1N1 Influenza

Suspected case: A person with acute febrile respiratory illness (fever 38°C) with onset within 7 days of close contact with an individual who is a confirmed case of H1N1 virus infection/or within 7 days of travel to areas where there is one or more confirmed H1N1 cases, or resides in a community where there is one or more confirmed swine flu case.

Probable case: An individual with an acute febrile respiratory illness who is positive for influenza A, but unsubtypable for H1 and H3 by influenza RTPCR or reagents used to detect seasonal influenza virus infection, or is positive for influenza A by influenza rapid test or influenza immunofluorescence assay (IFA) plus meets criteria for a suspected case, or an individual with a clinically compatible illness who died of an unexplained acute respiratory illness who is considered to be epidemiologically linked to a probable or confirmed case.

Confirmed case: A person with an acute febrile respiratory illness with laboratory confirmed swine influenza A (H1N1) virus infection by one or more of the following tests:

- Real time PCR
- Viral culture
- Four-fold rise in H1N1 virus specific neutralizing antibodies.

For confirmation of diagnosis, clinical specimens such as nasopharyngeal swabs, nasal swab, wash or aspirate and tracheal aspirate (for intubated patients) are to be obtained. Paired blood samples at an interval of 14 days for serological testing should be collected.

Management

1. ***Critical measures*** – (a) Avoid crowding patients together. (b) Hand hygiene. (c) Wear personal protective equipments which include high efficiency masks (ideally N95 mask or triple layer surgical mask), gowns, goggles, gloves, cap and shoe cover. (d) If suspected swine flu, isolation of infected individuals and household contacts.

Antiviral drug therapy: The two influenza drugs are neuraminidase inhibitors.

Oseltamivir is the recommended drug for prophylaxis and treatment (Table 7). It inhibits neuraminidase which is a glycoprotein on the surface of influenza virus that destroys an infected cell's receptor for viral haemagglutinin. The drug must be administered within 48 hours of symptom onset.

Side effects – The drug is usually well tolerated. GI side - effects (transient nausea, vomiting) increase with increasing doses. Occasionally it may cause bronchitis, insomnia and vertigo, rarely anaphylaxis and skin rashes. The most frequent adverse effect in children is vomiting.

Zanamivir is a sialic acid analogue that potentiates and specifically inhibits the neuraminidases of influenza A and B viruses. Inhaled zanamivir for the prevention and treatment for influenza virus infections. Early treatment with dose 10 mg bd for 5 days of febrile influenza in ambulatory adults and children aged 5 years and older shortens the time of illness resolution by 1–3 days and in adults reduces by 40% risk of lower respiratory tract complications.

Discharge policy – Adult patients should be discharged 7 days after symptoms have subsided, and children 14 days after. The family of patients discharged should be educated on personal hygiene and infection control measures at home.

Vaccines – (a) H1N1 nasal vaccine. Side effects are dryness of nose, fever and cold and changed sense of smell and taste and mild fever. (b) Injectable vaccine. The vaccine takes up to 3 weeks for antibodies to develop. Indication for prophylactic vaccination in high risk category - (i) Pregnant women because of higher risk of complications and can provide protection to infants. (ii) Household contacts and caretakers for infants < 6 months old, because of higher risk of complications. (iii) Healthcare services workers.

Table 7: Dosage of oseltamivir

Body weight	*Dose*
For prophylaxis od for 10 days	
<15 kg	30 mg
15–23 kg	45 mg
23–40 kg	60 mg
>40 kg	75 mg
For treatment bd for 5 days	
<15 kg	30 mg
15–23 kg	45 mg
23–40 kg	60 mg
>40 kg	75 mg

HERPES VIRUSES

The herpes viruses are diverse and there are major differences between members of the group; however, they have many features in common.

Characteristics of herpes viruses

- Large dsDNA genome
- Characteristic appearance on electron microscopy
- Initial infection often asymptomatic
- Establish latency, persists for life of individual
- Most reactivations are asymptomatic
- Reinfections also occur
- Most herpes viruses cause more than one disease
- Interfere with immune responses

Pathogenesis – Possible mechanisms for diseases caused by herpes viruses:

- Disease may result from virus replicating in cells and destroying them by lysis (e.g. chickenpox)
- An immunologically mediated disease may develop from the host immune response to herpes virus, e.g. CMV pneumonitis and erythema multiforme triggered by herpes simplex virus reactivation.
- The virus may precipitate rearrangements of host chromosomes, such that endogenous oncogenes are activated to produce a malignant phenotype (e.g. E-B virus, Burkitt's lymphoma).

Because each herpes virus has potential to interact in multiple ways with the host, each virus can cause more than one disease.

Herpes virus infections cause different clinical conditions listed in Table 8.

α-herpes Viruses

Herpes simplex virus 1 – is spread readily within families by salivary contact. Primary infection may cause stomatitis, but is usually asymptomatic. The virus establishes latency in dorsal root ganglia supplying the trigeminal nerve. Reactivation of the viral genome may be caused by ultraviolet light, stress or menstruation. Centrifugal axonal passage of virus particles may be perceived by the patient as a prodromal tingling, 24 hours before vesicular eruption on skin. HSV replicates in the skin for 1–3 days after which epithelial cells migrate from the lesion edge to repair the damage.

Table 8: Major diseases caused by herpes viruses

Virus	*Children*	*Adults*	*Immunocompromised*
α-herpes viruses			
Herpes simplex type 1	Stomatitis	Cold sores	Dissemination
		Keratitis	
		Erythema multiforme	
Herpes simplex type 2		Primary genital herpes	Dissemination
			Bed sores
Varicella zoster virus	Chickenpox	Recurrent herpes	Dissemination
	Shingles (in elderly)		
β-herpes viruses			
Cytomegalovirus	Congenital (mental retardation)		Pneumonitis
			Retinitis
			Enteritis
			Encephalitis
Human herpes virus type 6	Roseola infantum, febrile fits		Encephalitis
Human herpes virus type 7	Roseola infantum		
γ-herpes viruses			
Epstein-Barr virus		Infectious mononucleosis	Lymphomas
Human herpes virus type 8			Kaposi's sarcoma

In patients with eczema, scratching can introduce the virus at multiple sites causing a chickenpox-like rash termed 'eczema herpeticum'.

Herpes simplex virus 2 – is the main cause of genital herpes.

β-herpes Viruses

Cytomegalovirus – Congenital CMV can cause mental retardation and hearing loss. In the immunocompromised CMV causes systemic infection, with high mortality from pneumonitis and high morbidity from retinitis and enteritis.

γ-herpes Viruses

Epstein-Barr virus – Infection is usually acquired asymptomatically during childhood. If primary infection is delayed until adolescence, it may be accompanied by infectious mononucleosis.

Infectious mononucleosis ('glandular fever') is an acute, self-limiting febrile illness caused by primary EBV infection (Table 9).

Mode of transmission – Virus particles are present in pharynx and saliva during acute stage, and transmission occurs by close contact, e.g. kissing, sharing eating utensils, can be transmitted by blood transfusion.

Table 9: Causes of acute infectious mononucleosis syndromes

- Epstein-Barr virus
- Influenza A and B viruses
- Cytomegalovirus
- Human herpes virus 6
- Rubella virus
- HIV
- Coxiella burnetti
- Adenovirus
- Hepatitis A virus

Incubation period – 30–45 days.

Clinical Features

Pharyngitis is usually diffuse. An exudate is present in about 1/3 of cases. Palatal petechiae may occur.

Fever – Temperature may be high and may last 1–2 weeks.

Lymphadenopathy usually occupies the anterior and posterior cervical chains and may be diffuse.

Prodromal symptoms include malaise, anorexia, fatigue, headache and fever, all of which persist through the acute phase of illness.

Symptoms of EBV-IM usually peak 7 days after their onset and dissipate over the next 1 to 3 weeks.

Splenic enlargement is common.

Less common clinical features include upper airway obstruction, abdominal pain, hepatomegaly, jaundice, and eye lid oedema. Rash occurs in about 5% and may be macular, petechial, scarlatiniform, urticarial or erythema multiforme. A pruritic maculopapular rash develops in majority of patients who receive ampicillin, 7 to 10 days after administration. Frequency of jaundice varies with age.

Investigations

1. **Haematology** – WBC count usually increased. Absolute ($> 4 \times 10^9$) litre) and relative (> 50% of total WBC), increase in mononuclear cells of which up to 20% are atypical lymphocytes.
2. **Serology**

   Nonspecific heterophile antibodies – Patients with primary EBV infection develop IgM antibodies that bind antigens on RBCs of other species, particularly sheep and horses, but not guineapig kidney cells. Heterophile antibodies also occur in normal sera and in some patients with lymphoma, but these normally also bind to guinea pig kidney cells. These differences form the basis of tests for heterophile antibodies:

   (a) *Paul-Bunnell test* – measures agglutination of sheep RBCs by patient's serum.

   (b) *Modified Paul-Bunnell-Davidson test* – The serum is pre-absorbed with guinea pig kidney cells.

   (c) *Monospot test* – measures agglutination of formalinized horse RBCs after absorption with guinea pig kidney cells.

   Interpretation – Heterophile antibodies are present in 40% of patients during first week of illness. sixty percent by 2nd week and 80% by 3rd week; a negative monospot test hence does not exclude diagnosis of IM. After classical IM, heterophile antibodies usually persist for 3–6 months, and at times up to one year.

   Specific antibody responses – Patients also develop specific antibodies against – (a) Viral capsid antigen. Anti-VCA IgM is specific indicator of acute infection. Anti- VCA IgG is usually present at presentation and persists for life. (b) EBV early antigens (EA). (c) EBV nuclear antigens (EBNA). These tests may be helpful in difficult cases.
3. **Biochemistry** – Mild derangement of LFTs.

Complications

1. *Autoimmune hemolytic anaemia* – rare. Spontaneous resolution. Rarely thrombocytopenia with bleeding. Splenic rupture.
2. *Neurological* – Encephalitis with predominant cerebellar features, viral meningitis, Guillain-Barre syndrome, Bell's palsy, transverse myelitis.
3. *Other complications* – Cardiac – Nonspecific ECG changes, pericarditis.

Management – is mainly symptomatic. Initial period of bed rest for 2–3 weeks. Gargles with soluble aspirin helpful for relieving sore throat. Antibiotics such as erythromycin if secondary infection. Ampicillin should be avoided as it produces a rash. Corticosteroids if severe pharyngitis, airway obstruction, severe thrombocytopenic purpura or acute hemolytic anaemia, and polyneuritis. Infusions of EBV-specific cytotoxic T cells have been used to prevent EBV lymphoproliferative disease in high-risk settings as well as to treat the disease. Interferon α administration, cytotoxic chemotherapy and radiation therapy (especially for CNS lesions) also have been used.

Burkitt's lymphoma – In Africa, EBV cause Burkitt's lymphoma in children in patients with HIV infection, which is immunosuppressive and provides a mitogenic signal to the B cells harbouring EBV. It also causes lymphoma in immunocompromised patients, and is implicated in Hodgkin's disease and other sporadic lymphomas.

Antiviral Agents

Antiherpes treatment is summarized in Table 10.

Acyclovir – is effective and without significant side-effects. The specificity is because the phosphorylation required for its activation occurs only in cells infected with herpes viruses. In case of HSV and VZV, the viral thymidine kinase enzyme phosphorylates acyclovir. Acyclovir monophosphate is further phosphorylated to the triphosphate by cellular enzymes; the triphosphate becomes incorporated into the growing DNA chain and acts as an obligate chain terminator so inhibiting the DNA polymerase of all herpes viruses. It also inhibits the enzyme directly.

Ganciclovir and penciclovir – are activated in a similar manner but have adverse effects. Ganciclovir can cause significant bone marrow depression and is only advised for life or sight threatening CMF infections. Penciclovir is well tolerated clinically.

Table 10: Recommendations for antiherpes drugs

		First-line	*Alternative*
Herpes simplex virus	Immunocompromised	IV acyclovir	
	Encephalitis	IV acyclovir	
	Initial genital	Oral acyclovir	Famciclovir
	Recurrent genital	Oral acyclovir	Famciclovir
	Prophylaxis genital	Valaciclovir	Oral acyclovir
Varicella zoster virus	Immunocompromised	IV acyclovir	Oral acyclovir
	Chickenpox	IV acyclovir	Valaciclovir
	Zoster		
	Ophthalmic	Valaciclovir	Famciclovir
	Elsewhere	Valaciclovir	
Cytomegalovirus	Immunocompromised		Oral acyclovir
	Prophylaxis		
	Bone marrow transplant	Valaciclovir	
	Liver transplant	Oral ganciclovir	
	Kidney transplant	Valaciclovir	
	Retinitis in AIDS	IV foscarnet	IV ganciclovir
	Neonate with CMV inclusion disease with CNS involvement	IV ganciclovir	

Prodrugs – The bioavailability of the above compounds can be improved by use of prodrugs. Famciclovir is the prodrug of penciclovir and valaciclovir of acyclovir. After activation by virus thymidine kinase, penciclovir persists intracellularly for significantly longer than acyclovir, yet the latter is more potent inhibitor of DNA polymerase.

Foscarnet – is used i.v. for cytomegalovirus retinitis and induction therapy for mucocutaneous HSV unresponsive to acyclovir. Side effects are renal impairment and anaemia.

Purine analogues – *Ribavirin* inhibits DNA and RNA viruses, and is active against influenza, respiratory syncytial, herpes simplex. It can inhibit hepatitis B replication in chronic hepatitis B carriers. Aerosol form is indicated for RSV bronchiolitis or pneumonia, severe influenza and among immunocompromised for parainfluenza and measles. IV formulation has been used in Lassa fever, and haemorrhagic fever with renal syndrome due to Hantaan virus.

Tricyclic amines – *Rimantadine* and *Amantadine* inhibit influenza A virus. They are not recommended for children below 10 years. They can also be used for herpes zoster.

VIRAL MENINGITIS

Etiological agents of viral meningitis are listed in Table 11.

Clinical features: of viral meningitis.

Table 11: Causes of viral meningitis

- Mumps
- Enteroviruses (most important)
  - Poliovirus types 1, 2 and 3
  - Coxsackie virus type A
  - Coxsackie virus type B
- Echovirus
- Others
  - Enterovirus 71 (hand, foot and mouth disease)
  - Enterovirus 70 (epidemic conjunctivitis)
- Genital herpes simplex virus types 1 and 2
- Other herpes viruses
  - Cytomegalovirus
  - Epstein-Barr virus
  - Varicella-Zoster virus
- HIV
- Lymphocytic choriomeningitis virus
- Adenovirus types 3 and 7
- Arboviruses

Acute onset of fever, headache and accompanying signs of meningeal irritation. Nonspecific symptoms

include arthralgia and myalgia, sore throat, weakness and lethargy. Other symptoms and signs are specific for the causative agent.

Transmission – usually by droplet infection, close personal contact or faeco-oral contact.

Enteroviruses – comprise 70 serotypes, including polio virus, Coxsackievirus A and B, and echovirus. Most infections are asymptomatic. A rash may occur, erythematous and maculopapular, vesicular on palms, soles and feet and inside the mouth (as in hand, foot and mouth disease) or an exanthema in the oral cavity. Enterovirus serotype 71 can also induce acute flaccid paralysis identical to that caused by poliovirus.

HSV and Varicella-Zoster virus – Primary genital HSV infection can be associated with meningitis. A syndrome of benign recurrent aseptic meningitis has been shown to be caused by reactivation of genitally acquired HSV infection, most commonly HSV-2. This syndrome occurs predominantly in women. Average number of episodes is four. Headache may be associated with genital recurrence. Recurrence of VZV usually presents as shingles, but can also present as meningitis without a cutaneous component.

Mumps virus – Mumps meningitis occurs about 7–10 days after onset of parotitis. However the epidemiology has changed considerably after introduction of MMR vaccine.

Rotavirus. Rotaviruses are members of the family Reoviridae. Human illness is caused primarily by group A.

Pathogenesis. Rotaviruses infect and in the end destroy mature enterocytes in the villous epithelium of the proximal small intestine which together with proliferation of secretory crypt cells leads to secretory diarrhoea.

Cl. Fs.: GI - After incubation period of 1–3 days there is abrupt onset of vomiting followed by watery diarrhoea, fever. The symptoms subside within a week. In severely immunodeficient children or individuals after bone marrow transplant, there can be protracted diarrhoea with protracted viral excretion, and rarely can disseminate systemically.

Diagnosis can be confirmed by EIAs or by detecting viral RNA by gel electrophoresis, probe hybridization, or PCR.

Tr. is supportive with IV fluids.

Vaccine - Bovine-human reassortant vaccine containing serotypes G1, G2, G3, G4 and G9.

HIV – Headache occurs in about 50% of patients during primary HIV infection, and meningism is not uncommon. Higher HIV RNA levels correlate with neurological symptoms.

Table 12: Causes of viral encephalitis

Worldwide distribution
• Herpes simplex virus
• E-B virus
• Cytomegalovirus
• Varicella-Zoster virus
• Human herpes virus 6
• Non-polio enteroviruses
• Mumps virus
• Rabies virus
Geographically limited
• Western equine virus
• Eastern equine virus
• California encephalitis
• St. Louis encephalitis
• Japanese encephalitis
• Tick-borne encephalitis

VIRAL ENCEPHALITIS

Viral encephalitis is infection of brain parenchyma. It is also an uncommon outcome of many viral infections. Mortality is high, and there is long-term morbidity in many survivors. Infection can occur at any time from neonatal period to old age (Table 12).

Pathogeneses of infection – Viruses may reach CNS by:

Haematogenous route – used by arthropod - borne viruses, after injection into capillary blood by a tick or mosquito bite. Local replication in the surrounding skin is followed by primary viraemia. A secondary bout of multiplication produces secondary viraemia, which, if of sufficient magnitude, can cross the blood-brain barrier via infected WBCs or locally in vascular endothelia.

Neuronal route of entry – Examples are rabies and HSV which are transported directly into the brain by retrograde axoplasmic flow. This is a viral immune evasion mechanism – once inside the axon, the virus is invulnerable to immune control.

Clinical features – Onset is commonly acute, with fever, and headache. Because of injury to the brain, there are disturbances of higher mental function – confusion, delirium, behaviour changes, dysphasia/aphasia, temporal lobe seizures, focal neurological signs proceeding to coma. These distinguish viral encephalitis from meningitis, in which there is no nervous involvement.

Herpes simplex encephalitis – About two-thirds of cases are caused by virus reactivation; the remaining are caused by primary infection of the neonatal period (when HSV infection occurs during labour) or in childhood.

The virus accesses CNS via olfactory ganglia, but there is evidence for direct reactivation of latent virus within the brain. HSV has a particular affinity for the temporal lobe and, because it is cytolytic, considerable destruction of nervous tissue occurs. The site of replication is then reflected in the symptoms – temporal lobe seizures, speech disorders, personality changes and altered behaviour.

Infection in the immunocompromised – A slightly different (mostly latent) virus is responsible for encephalitis. CMV and VZV may lead to encephalitis and granulomatous arteritis with spinal cord myelopathy caused by CMV in HIV-infected patients. Such patients also suffer from replication of E-B virus and JC virus, leading to primary CNS lymphoma and progressive multifocal leucoencephalopathy respectively.

Diagnosis

CT – of head prior to LP to exclude space-occupying lesions and to reveal radiographic evidence of raised intracranial pressure. This is particularly important when herpes simplex encephalitis is suspected.

CSF – Typical findings in viral meningitis and encephalitis are pleocytosis, mildly elevated protein (0.5–1 g/L) and normal CSF: blood glucose ratio, and with predominant lymphocytes.

PCR analysis – can detect non-culturable enterovirus serotypes and results are available rapidly. In multiplex PCR analysis, as many as six different viruses may be tested for simultaneously.

Management

Viral meningitis – Prognosis is good in most cases. Treatment is supportive and includes adequate analgesia. Serious complications include unilateral deafness after mumps meningitis, chronic enterovirus meningitis in patients with agammaglobulinaemia, and hydrocephalus after intrauterine infection with lymphocytic choriomeningitis virus. Acyclovir for meningitis associated with primary genital herpes.

Herpes simplex encephalitis – Treatment should be started immediately after the diagnosis is suspected. Acyclovir 10–15 mg/kg i.v. t.d.s Relapse occurs in up to 5% patients, requiring continuation of treatment for at least 10–14 days.

PARVOVIRUS B19

Epidemiology – Common between 5–15 years. One attack confers life-long immunity. Parvovirus B19 is not as infectious as varicella, but school outbreaks are not uncommon. Spread is by respiratory droplet.

Clinical features – Mild febrile illness with coryza followed by a lacy, reticular rash with widespread arthralgia 7–10 days later. Arthralgia, often without a rash, is the most common presenting symptom in adults, particularly women. In children the rash is most prominent on the face (slapped cheek syndrome - erythema infectiosum). Arthralgia generally persists for a few weeks.

Special syndromes – The virus has the ability to replicate in erythroid progenitor cells in the bone marrow; this underlines three important clinical syndromes:

***Polyarthropathy Syndrome*:** Although uncommon among children, arthropathy occurs in 50% of adults and is more common among women than among men. The distribution of the affected joints is often symmetrical with arthralgia affecting the small joints of the hands and occasionally the ankles, knees and wrists.

Aplastic crises – In patients with reduced RBC survival (e.g. sickle cell disease, thalassemia, hereditary spherocytosis), a catastrophic decrease in haemoglobin occurs during acute B19 infection.

Transfusion-dependent anaemia – is seen in immunocompromised patients (e.g. bone marrow and solid organ transplantation, HIV infection). These patients require treatment with i.v. immunoglobulin, often over several weeks, because they are unable to mount a neutralizing antibody reaction to clear virus from bone marrow.

Pregnancy – B19 infection leads to miscarriage in 10% of cases, and there is additional 3% risk of foetal hydrops, though only when maternal infection occurs in first 20 weeks of gestation.

Diagnosis – relies on serology and virus detection using molecular methods. Virus-specific IgM is detectable from onset of rash/arthralgia, and persists for 2–3 months. In foetal hydrops and transfusion-dependent anaemia, detection of virus by DNA hybridization assays is preferable.

ADENOVIRUS INFECTIONS

Epidemiology – Adenoviruses are DNA viruses. There are 40 different adenovirus serotypes classified into six groups (A–F). Group C serotypes 1, 2 and 5 are primarily associated with respiratory disease. Transmission occurs via aerosol particles, faeco-oral route or contaminated fomites.

Clinical features – vary with age and presence of immune dysfunction (Table 13).

Investigations

Viral culture is the most sensitive method. The virus may be cultured from throat, nasopharynx, conjunctiva, sputum, urine, stool, CSF, blood or tissue specimens.

ELISA – is not as sensitive as viral culture but more rapid.

Histopathology – Presence of characteristic internuclear inclusions in tissue sections. When these enlarge and obscure the nuclear membrane, the cells are termed 'smudge' cells.

Serology – A fourfold increase in titre between paired sera is needed to confirm recent infection.

Management: Most adenoviral diseases are self-limiting and treatment is supportive. Bacterial superinfection may occur.

Table 13: Adenovirus infections in various groups

Infants
• Pharyngitis, coryza, pneumonia
• Otitis media
• Diarrhoea
Children
• Upper resp. disease, pneumonia
• Pharyngoconjunctival fever
• Diarrhoea, mesenteric adenitis
• Haemorrhagic cystitis
Young adults
• Acute respiratory disease
Adults
• Epidemic keratoconjunctivitis
Immunocompromised patients
• Pneumonia
• Gastroenteritis
• Hepatitis
• Meningoencephalitis

4. ACUTE CHILDHOOD EXANTHEMAS

MEASLES

Epidemiology

Age – mostly children between ages of 3 and 5 years, rare during first 6 months of life because of transferred passive immunity from mother. *Causative agent* – RNA paramyxovirus group. *Transmission* – Highly infectious and spread by direct contact or droplet infection. Patients suffering from measles shed virus from their respiratory tract during the prodromal period and for 24–48 hours after the rash appears. *Immunity* – Immune response is not fully competent in early infancy; intercurrent infection or malnutrition further reduce these responses, increasing severity of the disease. Transplacental maternal IgG provides protection during the first 3–6 months of life.

Incubation period – 8–10 days.

Period of infectivity – From onset of prodromal period to 4 days after appearance of rash.

Clinical Features

Illness of infection – Febrile catarrhal attack with fleeting rash in a few hours after exposure to measles.

Prodromal stage – usually 4–5 days.

- *Fever* – Abrupt rise of temperature to about 40°C (102°F).
- *Catarrh* – Coryza, conjunctivitis, photophobia and hacking cough.
- *Koplik's spots* (Enanthema) pathognomonic. Appear on 2nd day as minute pin-point bluish white specks with slight reddish mottled areola around them, on buccal mucosa usually opposite lower molars. They look like grains of salt. Variable in number. Occasionally large spots, few in number. The spots begin to fade with appearance of rash. Red blotches may be seen on soft palate. Koplik's spots may sometimes occur in the lower lip in front of the lower incisors, and in severe cases the palate and rest of the mucosa are peppered with these spots.
- *Laryngeal involvement* – Hoarseness and laryngeal stridor.
- *GI* – Persistent vomiting and diarrhoea.
- *Fleeting rashes* – either urticarial or erythematous.

Exanthematous stage – (a) *Rash* – On 5th day, red macules appear first behind ear, along hair line and on posterior parts of cheeks and spread rapidly in a few hours all over the body. Macules appear in crops which by confluence form blotches with crescentic or thumb nail edge. Fully erupted rash deepens in colour, petechiae may occur. In severe measles the rash is confluent, the face is swollen and disfigured and together with the photophobic eyes creates the typical measly appearance. (b) *Mucous membrane involvement* – includes conjunctivitis, rhinitis, stomatitis, laryngitis, tracheitis and bronchitis. There may also be gastroenteritis.

Stage of defervescence – Temperature falls by crisis or rapid lysis in 24 to 48 hours. Rash fades from face

downwards in same sequence as its appearance, and leaves brown staining often followed by branny desquamation. The more severe the measles, greater the extent of desquamation. At times the normal rash of measles instead of fading becomes a deep purple (purpuric measles) and this may persist for a week or two.

Varieties

1. *Modified measles* – In measles modified by gamma globulin or measles vaccine all symptoms and signs may be suppressed except the rash in the form of discrete macules scattered over the trunk.
2. *Measles in adults* – Constitutional symptoms may be more severe but less tendency to complications.
3. *Atypical measles* – in children who have received measles vaccine. Fever with petechial rash and oedema on lower legs and dorsum of feet.
4. *Morbilli bullosi* – Severe variety in which some of the lesions become bullous. May occur in malnourished children.
5. *Haemorrhagic measles (black measles)* – Haemorrhages into skin and bleeding from any or all of the body orifices.

Complications

1. *Secondary bacterial otitis media.*
2. *Pneumonia or bronchopneumonia* – main cause of death. During the latter part of exanthematous stage, combination of measles and adenovirus infection produces most severe symptoms and prolonged course.
3. *Laryngotracheobronchitis* (croup) – due to measles virus. May give rise to stridor.
4. *Herpes simplex gingivostomatitis* – Vesicles in mouth which rapidly ulcerate causing fever, salivation and difficulty in feeds. Disseminated herpes is rare.
5. *Acute post-infective encephalitis* – is the most common neurological complication. Headache, confusion, coma and convulsions result from autoimmune demyelination.
6. *Hepatitis* – usually in young adults with severe disease. Frank jaundice may occur. May be giant cells in the liver. Spontaneous resolution.
7. *Blindness* – In patients with protein energy malnutrition, combination of vitamin A deficiency and herpes simplex virus infection of the cornea may cause blindness.
8. Late complications – (a) Bronchiectasis. (b) Immunosuppressive measles encephalopathy – 1–6 months after an attack of mild or atypical measles in children receiving cytotoxic drug therapy. Neurological damage is severe. (c) Subacute sclerosing panencephalitis (SSPE) – It occurs about 3–12 years after infection, with altered behaviour and personality, intellectual decline, seizures and motor disturbances. Interferons promote viral maturation and may be used to slow clinical progression of SSPE. (d) Measles inclusion body encephalitis (MIBE) is a rare but fatal complication that affects individuals with effective cellular immunity and typically occurs months after infection.

Post-measles state – results from powerful immunosuppressive effect which alters immunity and the tissue-destructive effect of measles.

Clinical features – Gradual deterioration into chronic illness. (a) Growth retardation and diarrhoea – often with anorexia. May precipitate protein-energy-malnutrition. (b) Gingivostomatitis – with oral herpes, persistent pyrexia, worsening pneumonia, increasing hepatomegaly and encephalopathy. (c) Corneal ulcers mainly in malnourished children. (d) Other uncommon complications – Gangrene of tips of fingers and toes, cancrum oris, septicaemia, candidosis, reactivation of pulmonary tuberculosis, possibly abortion or prematurity if infection occurs during pregnancy.

Diagnosis – Precise diagnosis can be achieved by using antigen detection in the saliva (enzyme-linked immunosorbent assay), immunofluorescence for antigen in bronchoalveolar lavage specimens, traditional paired serology and presence of IgG antibodies in the CSF if suspected in subacute sclerosing panencephalitis (SSPE).

Differential Diagnosis

Pre-Exanthematous stage – Common cold, influenza, catarrhal stage of whooping cough.

Exanthematous stage

1. *Rubella* – No Koplik's spots, small shotty enlargement of suboccipital, posterior cervical and post-auricular lymph nodes; catarrhal symptoms and systemic disturbances slight. In measles, mucous membrane is infected and dirty, in rubella it is pale and clean.
2. *Drug eruption* – especially that caused by ampicillin. Tends to persist longer and may have an urticarial element. Absence of catarrh and failure of rash to evolve from above downwards.
3. *Serum rashes* – Rash dense at site of injection, typical wheals.
4. *Infectious mononucleosis* – Fever, adenopathy and sore throat. Maculopapular rash, splenomegaly. Atypical lymphocytes in blood smear.

5. *Erythema infectiosum* – Rash but usually no constitutional symptoms. Rash appears in three phases. It begins with livid erythema of the cheeks (slapped cheeks), followed by maculopapular rash on extremities and trunk, and as the rash fades it has a lacy reticular appearance.
6. *Roseola infantum* (Exanthema subitum) – Acute viral disease of young children. three to four days of high fever. As fever falls by crisis, a pleomorphic, macular, erythematous rash appears on face and trunk and fades in 1–3 days.
7. *Erythema multiforme* – Circular or irregular erythematous blotches usually occurring on backs of hands and forearms. Constitutional symptoms may be present.
8. *Other exanthemas* – (a) Coxsackie virus A. Hand-foot-and-mouth disease is the most specific syndrome. After a short prodrome of malaise, anorexia and fever, a vesicular enanthem develops involving buccal mucosa. A vesicular exanthem also appears on hands and feet in many patients. (b) Other viral infections – Adenovirus, parainfluenza virus, respiratory syncytial virus may occasionally be associated with macular or maculopapular rashes.
9. *Paratyphoid* – Sometimes profuse pinkish brown maculopapules. Longer prodromal illness, characteristic temperature chart, agglutination test positive.
10. *Typhus* – Early prostration; mental symptoms; rash bright red, subcuticular mottling, no well-defined edges, not marked on face. Eschar.
11. *Scarlet fever* – Short prodromal period, sore throat, anterior cervical adenitis, scarlet rash, circumoral pallor and punctuate haemorrhages. Skin folds in groin, neck, axillae and knees become dark red (Pastia's lines). Circumoral pallor is common and skin often has a fine sandpaper texture. Strawberry tongue.
12. *Kawasaki disease* – Fever, conjunctival congestion, erythema of lips, buccal mucous membrane and tongue. Acute cervical lymphadenopathy, polymorphic exanthema, erythema of palms and soles.

Management

Frequent fluid intake. Paracetamol for fever. Irrigation of eyes with boric lotion. Cough linctus to suppress the dry cough. Antibiotics such as amoxicillin if complications such as otitis media or pneumonia. Should be given prophylactically to 'poor-risk' children. Vitamin A 200,000 IU orally for 2 days, will prevent ocular complications and reduce respiratory infections and measles-related mortality.

Antiviral treatment (ribavirin) for viral pneumonitis. Acyclovir may be used to treat secondary herpetic infection. Antifungal therapy (e.g. fluconazole) for oral and intestinal candidosis (anaphylactic egg-protein hypersensitivity).

Prevention

(a) Active immunization – (i) Single dose of attenuated live-virus vaccine for all children at the beginning of second year of life. *Contraindications* – Personal history of convulsions, intercurrent illness or recent exposure to other infectious disease, those receiving corticosteroids, or other immunosuppressive agents, leukaemia, tuberculosis, and in any stage of pregnancy. *Untoward effects* – Febrile reaction after one week, sometimes rash. Rarely convulsions and very rarely encephalitis. (ii) Inhalation of measles vaccine aerosol, it takes the pathway taken by the viral antigen to enter the body thereby inducing a strong immune response.

(b) Passive immunization – with immunoglobulin is useful in debilitated patients in contact of measles patients followed in 3 months by vaccine. Dose 0.25 mL/kg IM. It should be given within 6 days of exposure.

RUBELLA (GERMAN MEASLES)

Rubella is an exanthema caused by a RNA virus of the togavirus family.

Transmission – Droplet inhalation from an infected person. Neonates with congenital infection are prominent shedders of the virus, which may be found, often as long as 6 months.

Incubation period – 14–21 days.

Period of infectivity – from 7 days before to 2 weeks after onset.

Clinical Features

Exanthem – Rash occurs more often in older children and adults on first or second day of illness, first on face and behind the ears, and then spreads downwards to trunk and limbs. The rash is variable but commonly starts as discrete, pink, punctate, erythematous, perifollicular macules that rapidly become confluent. Alternatively, there may be blotchy pink rash or confluent blush. The rash seldom persists for more than 4 days and is not followed by staining or desquamation. Rubella without rash is common in young children. In a dark-skinned patient all that may be seen is prominence of hair follicles giving a goose-pimpled appearance.

Arthralgia is common and occasionally arthritis. Distribution is usually symmetrical polysynovitis involving the small joints of hands, knees, hips and intervertebral joints, which occasionally may not remit promptly.

Lymphadenopathy – Slight enlargement of lymph nodes, particularly of suboccipital and posterior auricular groups.

Buccal mucous membranes – are inflamed, with blotchy erythema and prominent follicles on soft palate, (Forschheimer spots) accompanied by mild conjunctivitis and coryza.

Complications – are common and include encephalitis, G-B syndrome, thrombocytopenia and hepatitis.

Treatment – Bed rest and analgesics suffice for the uncomplicated attack. Rubella proven by antibody estimation in first 4 months of pregnancy is a strong indication for termination.

Strategies for Immunization

1. Combined MMR vaccine is given routinely to all children in the second year of life, with a booster in the second decade.
2. All women are screened when they reach childbearing age and are immunized with monovalent rubella vaccine, if non-immune. It is necessary to maintain adequate contraceptive measures for 3 months.
3. Routine screening and immunization are undertaken in the immediate postnatal period. Immunized mothers excrete the vaccine virus in breast milk for up to 1 month; this is not a contraindication to vaccination or breastfeeding.

Adverse reactions – to vaccine are limited and include transient arthralgia, and egg and neomycin hypersensitive reactions.

Congenital rubella syndrome – occurs when the foetus is infected during maternal viraemia (virus can be isolated from 90% of foetuses in infected pregnancies). The virus gains widespread access to foetal tissues, causing cytopathic effects or promoting immune response.

Defects – The consequences of rubella in pregnancy are varied and unpredictable, ranging from foetal death to birth of an infected but otherwise normal child.

1. Temporary defect – if cytopathic damage to non-organ tissue: (a) *Thrombocytopenic purpura* – at birth or shortly after. (b) *Hepatosplenomegaly*. (c) *Hepatitis*. (d) *Low birth weight*.
2. Permanent – when there is cytopathic effect in early organogenesis. (Triad of Gregg).
   - Cataracts and retinopathy.
   - Microcephaly.
   - Congenital heart defects (PDA with or without PS most common).

Late congenital rubella. In some infants, particularly those infected after the first trimester, there is no obvious congenital defect, but the infant sheds the virus. In this group, late congenital rubella features include:

- Quadriparesis
- Growth retardation
- Behaviour disorders
- Psychiatric manifestations
- High-tone deafness
- Insulin-dependent diabetes mellitus

Procedures to be adopted in a pregnant woman

(a) *Suspicion of having rubella* – Accurate diagnosis should be established by serological tests. If IgM is positive, explain the degree of risk to the patient and decide about termination of pregnancy.

(b) *Suspicion of having been in contact with rubella* – (i) If possible, confirm the diagnosis by serological studies on the original case. (ii) If contact is close and the pregnant woman has decided to continue with pregnancy give 1500 mg of immunoglobulin IM as soon as primary sample of serum is obtained. If there is no detectable antibody, give further 1500 mg immunoglobulin within 72 hours, it reduces but does not eliminate the risk of rubella. (iii) If she does not want to continue with pregnancy, or if the contact is not close, do not give immunoglobulin. (iv) In either case, take a second sample of blood after 3–4 weeks to see if there has been sero-conversion. The risk to the foetus when the mother has a subclinical attack is not known with certainty but appears to be slight. Should the mother develop an illness with serological evidence of rubella, the risks should be explained and decision taken about termination of pregnancy.

Immunization: Rubella vaccine live attenuated.

Parvovirus infection – has already been described.

Roseola infantum (exanthema subitum)

Aetiology and pathogenesis – Causative agent human herpes virus 6 at 6–24 months of age. It is a lymphocytic virus that targets CD_4+ cells and causes a common acute febrile illness of infancy. In adults, replication and elevated antibody titres are associated with lymphoid malignancies, SLE, Kikuchi's disease, atypical pneumonia, hepatitis, glandular fever-like illness and multiple sclerosis.

Reactivation of latent infection occurs in immunocompromised patients, particularly those who have undergone organ marrow transplantation or who have AIDS.

Clinical Features

Incubation period about 2 weeks.

Onset with high fever, coryza and cervical lymphadenopathy. After 2–4 days, fever settles and is followed by a pleomorphic, macular, erythematous, blotchy rash on face and trunk. The disease is seldom severe. Most patients have fever only, but the height of fever and CNS replication are associated with febrile convulsions.

Laboratory tests – At onset, there may be neutrophil leucocytosis, but this rapidly declines, leaving relative lymphocytosis. Serology is necessary to distinguish roseola infantum from other exanthemata.

CHICKENPOX

Epidemiology

Age – Primarily children, uncommon in adults in whom the disease tends to be more severe. *Causative agent* – Virus is identical to virus of herpes zoster and hence designated varicella zoster virus (V-Z virus). *Transmission* – Droplet discharges from air passages. May be direct skin contact or by recently contaminated utensils.

Incubation period – 14 to 15 days.

Period of infectivity –Patients are infectious 48 h before onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4–5 days) and until all vesicles are crusted.

Clinical Features

Stage of Invasion or Prodromata

not constant. Headache, sore throat and fever for 24 hours. Prodromal rashes – Erythematous, scarlatiniform, morbilliform or urticarial. Rarely haemorrhagic.

Stage of Eruption

1. Enanthem – Earliest lesions on buccal and pharyngeal mucosa.
2. Exanthem – (a) *Evolution* – in crops; at first back, then chest, abdomen, face, and lastly limbs. (b) *Character* – At first macule, in few hours' dark pink papule which soon turns into vesicle – (i) superficial, i.e. 'on' rather than 'in' the skin (glass pox), (ii) elliptical or oval ("tear drop" vesicles) with axis parallel to ribs, (iii) unilocular, hence collapse if pierced with a needle. Vesicles turn into pustules in 24 hours. Scabs in 2 to 5 days. (c) *Distribution* – centripetal, i.e. more on upper arms and thighs and upper part of face, and in concavities and flexures. Less commonly lesions on genital mucous membranes, conjunctivae and cornea. (d) *Cropping* – Rash matures very quickly and most spots dry up within 48 hours of appearance. But for 2-3 days' new spots continue to appear so that on any area of the body vesicles, pustules and scabs are found side by side (Polymorphism). In immunocompromised patients both children and adults, particularly those with leukaemia have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompetent patients.
3. Other symptoms – Pruritus of varying degree. Generalized lymphadenopathy may occur and enlargement of suboccipital and posterior cervical lymph nodes from secondarily infected scalp lesions.

Unusual Forms

1. *Varicella hemorrhagica* – Haemorrhages into vesicles, skin, subconjunctiva or from intestines. The complication is not due to overwhelming toxaemia as in smallpox but due to thrombocytopenia.
2. *Varicella bullosa* – Few or many of the lesions become bullous; common in children with impetigo.
3. *Varicella gangrenosa* – due to infection with hemolytic streptococcus producing the fulminating type, or with diphtheria bacillus causing the subacute type. Necrosis of lesions with toxaemia.
4. *Congenital and Neonatal chickenpox* – Virus may pass through the placenta and the baby is born with chickenpox or develops it in neonatal period.

Complications

(a) *Bacterial infection of skin* (usually group A streptococci or Staph.aureus) causing impetigo, cellulitis and post inflammatory scarring. (b) *Other uncommon complications* - The most common extracutaneous site of involvement in children is the CNS. The syndrome of acute cerebellar ataxia and meningeal inflammation generally appears - 21 days after onset of the rash and rarely develops in the pre-eruptive phase. Others are otitis media, pneumonia, cerebellar ataxia, Reye's syndrome and aseptic meningitis. Post varicella angiopathy is a rare complication which presents as acute hemiparesis, aphasia, hemianaesthesia or other focal neurological or retinal deficits with mononuclear pleocytosis. VSV specific antibodies in CSF. Varicella encephalitis usually appears 3–7 days after onset of rash with headache, fever, seizures, coma or paraplegia. Complications tend to be more severe in adults or in immunocompromised children.

Laboratory Diagnosis

A Tzazk smear, performed by scraping the base of an acute lesion and staining with Giemsa's or Papanicolaou's stain, may demonstrate multinucleated giant cells containing intranuclear inclusions. Other tests include fluorescent antibody against membrane antigen, immuno-adherence haemagglutination and enzyme-linked immunoabsorbent assay.

Differential Diagnosis

1. *Papular urticaria* – Haphazard distribution, face rarely invaded and mouth never, lesions appear in crops chiefly at night, intense itching, dietetic disturbances.
2. *Infected scabies* – Lesions never occur in mouth, face not affected except occasionally in children, identification of Sarcoptes scabiei from burrows.
3. *Impetigo contagiosa* – Mostly on face, mucous membranes not affected.
4. *Herpes zoster* – Unilateral distribution corresponding to nerve roots.
5. *Insect bites* – on the face, which have become septic. Central puncta.
6. *Dermatitis herpetiformis* – Erythematous papulovesicular and urticarial lesions markedly pruritic. Runs a chronic course with residual pigmentation.
7. *Rickettsial pox* – Appearance of primary lesion, influenza-like illness and generalized papulovesicular eruption.
8. *Bullous eruptions* – of bullous impetigo, pemphigus, and bullous form of erythema multiforme. Iodide or bromide or barbiturate rashes.
9. *Hand, foot and mouth disease* – Lesions involve mainly the palms, soles and oral mucosa and do not crust.

Complications

Rare in children. In adults the disease tends to be more severe and is more likely to be fulminant or complicated by pulmonary involvement.

1. *Cellulitis or impetigo* – due to secondary Strepto. or Staphylococcus infection from scratching of the lesions.
2. *Pneumonia* – (a) In children due to secondary infection. (b) Pneumonitis – due to VZ virus may complicate severe attacks, particularly in adults or in patients on long-term corticosteroid or immunosuppressive therapy. Chest X-ray shows large nodular opacities scattered throughout the lung fields.
3. *Neurological complications* – Post-varicella encephalitis more common in children than adults. Differs from other virus encephalitides because of predominance of cerebellar signs such as ataxia, vertigo, and nystagmus. Cranial nerve palsies particularly of oculomotor and facial nerves may develop. Reye's syndrome (particularly if aspirin has been given to the child), transverse myelitis and Guillain-Barre syndrome may also occur.
4. *Thrombocytopenia* – is sometimes seen after the rash has begun to heal. Probably due to megakaryocyte infection or unmasking of latent ITP.
5. *Congenital abnormalities* – very rarely in first trimester of pregnancy in the form of scarred and atrophied limbs, microcephaly and ocular damage.
6. *In the immunocompromised child* – Varicella is often severe and the rash and high fever continue for up to 2–3 weeks. Visceral involvement causing hepatitis, pneumonitis and encephalitis is common.

Management

1. No need to confine patient to bed unless symptoms are severe. 2. For pruritus – Calamine lotion with or without phenol (0.4%) and sedative antihistaminics by mouth. If there is much scabbing, gauze soaked in 1 in 5,000 solution of potassium permanganate which is changed every 4 hours may be applied to areas most affected. 3. For secondary infection – Antibiotics. 4. For true varicella pneumonia – Oxygen. 5. For encephalitis – Oxygen and corticosteroids. 6. Paracetamol for fever. Aspirin is contraindicated because of the association with Reye's syndrome. 7. Oral acyclovir initiated within 24h of rash results in a decrease in the duration and magnitude of the fever, and in the number and duration of skin lesions. Indications – High risk individuals such as healthy non-pregnant females 13 years of age or more, children older than 12 months with a chronic cutaneous or pulmonary disorder, children receiving long-term salicylate therapy, and possibly children receiving oral or inhaled corticosteroids. Dose – 20 mg/kg qds. with maximum of 800 mg qds.

Prevention

(1) *Varicella zoster immunoglobulin.* Indications: (a) Following significant exposure to chickenpox in immunocompromised and susceptible children. (b) Susceptible adolescents and adults, particularly pregnant women. (Patient should receive VZIG as soon as possible but not >96 h after exposure). (c) Newborn infants whose mothers have chickenpox within 5 days before delivery or within 48 hours after delivery. (d) Premature infants of less than 28 weeks gestation. (e) Premature infants whose mothers do not have a history of chickenpox. Dose – 125 units (1.25 mL)/10 kg body wt., i.m. within 48 hours and preferably not later than 96h after exposure. Maximum suggested dose is 625 units. (2) *Vaccine* – Live attenuated varicella

vaccine. Safe and highly protective in both healthy and immuno-compromised children. Adverse effects – Minor rash, often accompanied by fever. Dose: In children 2–12 years, who have not had chickenpox, two doses recommended the first at 12–15 months of age second at 4–6 years of age. VZV -seronegative persons > 13 years of age should receive two doses of vaccine at least 1 month apart.

5. MUMPS

AETIOLOGY

Age – Majority in children under 15. *Causative agent* – Paramyxoma virus. *Portal of entry* – Upper respiratory tract; it spreads through blood stream and has tendency to multiply in glandular structures. Spreads from human reservoir by direct contact, airborne droplet nuclei, or fomites contaminated by infected saliva.

Incubation period – 16–21 days.

CLINICAL FEATURES

Onset – (i) Moderate fever, sore throat, drawing or puckering feeling at angle of jaw. (ii) Swelling of face may be the first to draw attention. (iii) Onset with rigor or convulsion. (iv) With meningeal reaction – "cerebral mumps".

Early signs – (i) Pain or tenderness on pressure beneath angle of lower jaw. (ii) Reddening of parotid duct orifice.

Parotid glands – usually one gland affected followed by the other after a varying interval; or only one gland affected throughout; or simultaneous enlargement of both. The swelling reaches its maximum in about 3 days, remains at its peak for about 2 days and then slowly recedes. The lobe of the ear is in the centre of the swelling which is tender on pressure.

Fever – may rise to 40°C after appearance of parotitis; remittent, or intermittent, falls by lysis in 3–7 days.

Other symptoms – Diminished salivation, furred tongue and foul breath. Marked enlargement of parotid may cause trismus and deafness.

Other non-parotid mumps – Submaxillary and less frequently sublingual glands may enlarge, ovaries, pancreas, thyroid and breasts may be affected.

COMPLICATIONS

A. Common

1. *Orchitis and epididymitis* – usually unilateral. Common in young adults, may occur without parotitis. Fever returns and may go up to 40.5°C. Testis swollen, tender and tense with or without epididymitis. At the height of the attack delirium or stupor may occur. Lasts for about 10 days; may result in sterility.
2. *Meningitis* – Usually follows parotitis but may occur at the same time or even before salivary gland enlargement.
3. *Oophoritis* – Less common than orchitis. Bilateral suprapubic pain.
4. *Acute pancreatitis* – in 2nd week. Occasionally the disease presents with pancreatitis without salivary gland involvement. Diabetes may be a sequel.

B. Rare

1. *Neurological complications* – (a) Meningoencephalitis – as a rule appears 3-10 days after onset of glandular swelling, but sometimes precedes it and at times appears in absence of glandular swelling. CSF cell count often 50-200 × 10^6 lymphocytes/litre with slightly raised protein. (b) Cranial nerve involvement – Facial, and auditory, nerve deafness may be permanent. (c) Polyneuritis usually temporary. (d) Other CNS problems occasionally associated with mumps include cerebellar ataxia, facial palsy, transverse myelitis, hydrocephalus, Guillain–Barre syndrome, flaccid paralysis and behavioural changes.
2. *Arthritis* – Occasionally of one or more large joints, often the knee follows mumps, but no permanent damage results.
3. *Mastitis* – Mild and transient enlargement of breasts of either sex. *Prostatitis* – in males.
4. *Thyroiditis.*
5. *Nephritis.*
6. *Foetal endocardial fibroelastosis* – very occasionally during pregnancy, or if contacted in the first trimester, abortion.

DIAGNOSIS

(a) *Viral isolation* – from saliva or nasopharynx in acute illness or from CSF in mumps meningitis. (b) *Antibody titre* – Four-fold rise 1–2 weeks after infection.

DIFFERENTIAL DIAGNOSIS

1. Infection and inflammation

(a) *Acute suppurative parotitis* – Painful, swollen, tender gland with, oedema of subcutaneous tissues. Fever. Oedema and redness around orifice of parotid duct. Pressure over gland may produce flow of pus in mouth.

(b) *Recurrent parotitis* – usually unilateral. Constitutional disturbance slight. Gland may not be

enlarged, in quiescent stage but its limits are often palpable. X-ray after injection of lipiodol into ducts shows dilatation of ducts.

(c) *Chronic parotitis* – Late stage of recurrent parotitis due to recurrent exacerbations, or associated with calculus.

2. Obstruction – of major salivary ducts usually by salivary calculi, rarely by injury or tumour.
3. DRUG REACTIONS –Hypersensitivity to phenothiazines, thiouracil, iodides, thiocyanate, isoprenaline, copper, lead and mercury.
4. NEOPLASMS – So-called mixed tumour. A slow growing, nodular or rounded, painless and mobile swelling, usually unilateral.
5. Associated with systemic disease
   (a) *Sialosis* – Painless, soft, diffuse, non-tender enlargement of parotid glands may be associated with diabetes mellitus, cirrhosis, hyperlipoproteinaemia, anorexia nervosa.
   (b) *Sarcoidosis* – May rarely cause parotid enlargement. Dry eyes and xerostomia are common features.
   (c) *Sjögren's syndrome* – Firm, non-tender enlargement of parotid and submandibular glands which may vary in size over several weeks or may persist.
6. Miscellaneous
   (a) *Mikulicz's disease* – Bilateral chronic painless enlargement of parotid, and other salivary glands and lacrimal gland.
   (b) *Uveoparotid tuberculosis* – Bilateral swelling of parotid glands with inflammation of uveal tract. Lymph glands may be enlarged and spleen palpable. Gland firm, painless and often nodular. No reddening of orifice of Stensen's duct.

MANAGEMENT

1. *Diet* – Liquids, or semisolids depending on patient's ability to chew.
2. *Oral hygiene* – Frequent mouth wash.
3. *Paracetamol* – for pain and fever.
4. *Management of orchitis* – Complete bed rest, ice compress to scrotum, sling support for testicle. Prednisolone if swelling very severe 15 mg qds. for 4 days and then gradually tapered. Reduces testicular pain and swelling, but does not shorten duration of orchitis or lessen risk of testicular atrophy. If pain severe, incision of tunica vaginalis or injection of spermatic cord at the external inguinal ring with 10–20 mL of 1% procaine solution.
5. Mumps vaccine is not recommended over 6 years of age because reactions are more common in older children. Risk of vaccination (brain damage) can be reduced if vaccine is not given to infants with brain injury, CNS damage, personal or immediate family history of fits, or previous reaction to vaccine.

6. WHOOPING COUGH (PERTUSSIS)

EPIDEMIOLOGY

Age any, but mostly in children. Seasonal incidence. Sporadic and epidemic. Association with measles common. *Causative organisms* – Gram negative bacillus *Bordetella pertussis*, or less *commonly*, *B. parapertussis.* Spread – by droplet route.

Incubation period – 7–14 days.

CLINICAL FEATURES

Three stages, each lasting about 2 weeks.

1. CATARRHAL – Insidious onset with nonspecific symptoms such as rhinorrhoea, sore throat, conjunctivitis and non-productive cough.
2. SPASMODIC – The cough becomes paroxysmal and episodes of coughing may cause cyanosis or facial discoloration as a result of venous congestion. Paroxysms can occur several times per day and are common at night. They occur spontaneously or are precipitated by external stimuli such as noise or cold air.
3. Convalescent stage – About the 4th week, paroxysms diminish in intensity, child ceases to vomit, then to whoop, and finally to cough. Appetite returns with improvement in general nutrition.
   See Table 14 for the atypical features of pertussis.

LABORATORY INVESTIGATIONS

Culture – of secretions is highly specific, but 80% sensitive. A specimen is collected via a pernasal swab or by nasopharyngeal aspiration.

PCR analysis – is more sensitive than culture and specific.

Serology – Most widely used antigens are pertussis toxin and filamentous haemagglutinin and both IgA and IgG antibody response can be measured by enzyme-linked immunosorbent assay methods.

Lymphocytosis – is nonspecific.

COMPLICATIONS

Secondary infections are suspected when a new fever develops or symptoms, signs become apparent between paroxysms.

Table 14: Atypical features of pertussis
Infants
• Apnoea
• Cough (no whoop)
• Cyanotic episodes
• Vomiting
• Poor feeding
• Seizures
• Sudden infant death syndrome
Partially immunized
• Duration of catarrhal stage may be reduced
• Whoop may not occur
Adults
• Prolonged cough
• Paroxysmal cough
• Whoop
• Phlegm
• Posttussive vomiting

Table 15: Complications of pertussis
Secondary infections
Atelectasis
Post-pertussis bronchiectasis.
Otitis media may occur.
Weight loss and malnutrition
Physical effects of paroxysm
Subconjunctival and scleral haemorrhages
Facial and truncal petechiae
Epistaxis
Subcutaneous emphysema
Pneumothorax
Umbilical and inguinal hernias
Rectal prolapse
Urinary incontinence
Seizures
Rib fracture in adults
Disc herniation

- Bacterial pneumonia may be caused by vomiting and aspiration or local damaging effects of the organism.
- Atelectasis due partly to viscid mucus secretions and partly to bronchial and peribronchial inflammation (see Table 15).

DIAGNOSIS

A child presenting with classic symptoms of paroxysmal cough, posttussive vomiting and whoop is likely to have infection caused by *B. pertussis*. In older children it may be difficult to differentiate infections caused by other respiratory tract infections and cultures of nasopharyngeal secretions on appropriate media are necessary.

MANAGEMENT

General (a) Isolation in a well-ventilated room. (b) Feeding: Food finely divided and in small feeds. (c) During a paroxysm, child should be lifted from the cot and held in a head low position, patting the back until the spasm is over.

Feeds should be given immediately after vomiting which frequently follows a paroxysm of coughing.

Drugs – (a) Antibiotics: Erythromycin 50 mg/kg day in 3 divided doses for 7–14 days may reduce severity of infection. (b) Antispasmodic: Salbutamol liquid 1 mg tds.

Prevention: Erythromycin 40 mg/kg/day in 4 divided doses may prevent or modify whooping cough in the non-immune neonate who has been exposed to the disease. (For immunization schedule, see Diseases of Children).

DTaP vaccine, a cellular pertussis vaccine containing antigen components of B. pertussis may be available in future.

7. ENTEROVIRUS INFECTIONS

Classification: Enteroviruses are a large group of human pathogens and approximately 64 serotypes infect humans, including the polioviruses, group A and B, coxsackie viruses and echoviruses. Spread is via faeco-oral route. They can lead to a wide variety of clinical diseases given in Table 16.

POLIOMYELITIS

Paralytic poliomyelitis is, by definition, caused by one of the three poliovirus serotypes, though other, non-polio enterovirus may occasionally cause a similar syndrome. More commonly polioviruses cause aseptic meningitis or mild nonspecific symptoms.

Virology

Majority outbreaks of paralytic polio are due to type 1 poliovirus, however type 2 virus appears to be the most effective immunogen and thus the highest rate of seroconversion following immunization with the trivalent vaccine is to this type.

Table 16: Clinical entities associated with enterovirus infections

Organ system	*Clinical entity*	*Main serotypes involved*
CNS	• Paralytic Polio	Poliovirus 1-3
	• Aseptic meningitis	Numerous
	• Encephalitis	Numerous
Cardiac and skeletal muscle	• Myocarditis	Coxsackievirus
	• Dilated cardiomyopathy	Coxsackievirus
	• Pericarditis	Coxsackievirus
	• Bornholm disease	Coxsackievirus
Skin and mucous membrane	• Hand, foot and mouth disease	Coxsackie A16
	• Rash	Enterovirus 71
	• Herpangina	Numerous
	• Viral conjunctivitis	Coxsackievirus A
	• Acute haemorrhagic conjunctivitis	Numerous
Respiratory tract	• Summer cold	Enterovirus 70, coxsackievirus A 24
	• Nonspecific febrile illness	Numerous

Pathogenesis

Poliovirus enters GI tract by ingestion and then spreads to various organs of the body. Replication of the virus occurs in three phases:

Phase 1 – Primary replication occurs in the epithelial cells of the oropharynx and intestinal mucosa, and also in subjacent lymphoid tissue (the tonsils and Payer's patches). Substantial amplification of the virus does occur but this is insufficient to cause clinical symptoms.

Phase 2 – After primary multiplication, virus spreads via the draining lymphatics into regional lymph nodes (deep cervical and mesenteric lymph nodes) and undergoes further replication and amplification. It then enters the bloodstream and results in a transient viraemia which clinically manifests as a mild, febrile illness.

Phase 3 – Following the transient viraemia, virus is disseminated into various extraneural tissues, e.g. the brown fat and reticuloendothelial cells of a number of viscera. Here extensive replication of virus occurs; this continuously supplies the bloodstream and produces a persistent viraemia. From blood the virus passes to the central nervous system.

Infection of CNS occurs in majority. Virus reaches CNS via two routes – (a) Haematogenous, i.e. directly through capillary walls of CNS. (b) Neurological by travelling up the autonomic nervous system of the intestine.

Relationship of pathogenesis to clinical features – This method of spread within the body accounts for the four stages of the disease at any of which it may be arrested:

(a) *Silent infection* – Virus in alimentary phase.

(b) *Abortive poliomyelitis* – Virus in both alimentary and viraemic phases.

(c) *Non-paralytic polio* – Virus in alimentary, viraemic and neural phases.

(d) *Paralytic poliomyelitis* – Virus in all three phases, its action on neuron causing paralysis.

Clinical Features

1. **Prodromal stage** – Start of systemic phase of the infection. (a) *Respiratory* – Coryza, sore throat or cough. (b) *Gastrointestinal* – vomiting, diarrhoea or constipation, or (c) *Constitutional* – Fever, headache, drowsiness, restlessness, irritability and sweating. Temperature falls to normal in 36–48 hours and rises again as the pre-paralytic stage is reached, giving a double humped or dromedary chart.
2. **Preparalytic stage** – Start of neural phase of the infection. Symptoms and signs of meningeal irritation:

Symptoms

- Fever – Temperature rises to 39°C, associated back pain and stiffness.
- Headache – moderate.
- Nausea, vomiting may occur.
- Pains – spontaneous or provoked by movement of back, neck, limbs and sometimes abdomen.
- Cutaneous hyperaesthesia – may be present; generalized or localized presaging paralysis of that part.
- Nuchal and spinal rigidity – (a) Active tests – (i) Tripod sign – The child is made to sit up unassisted; the knees flex upward and the child places his hands on the bed behind him due to spinal rigidity. (ii) Kiss-the-knee test – Ask child to sit up and kiss his knees. He is able to do so only by flexing the knee. (b) Passive tests – (i) Positive Kernig's and Brudzinski's signs. (ii) Nuchal rigidity. (iii) Head drop sign – The head falls backward when the shoulders are elevated.
- Muscle fasciculation – may be observed.
- Micturition disturbance – Difficulty of micturition or retention of urine may occur.
- Reflexes – Superficial and deep reflexes – in early stages active and remain so unless paralysis supervenes.

Signs

- Pulse fast and out of proportion to rise of temperature.
- Excessive perspiration.
- Patient is alert.

3. **Paralytic stage** – usually develops between 2nd and 5th days after onset of signs of involvement of nervous system. May set in without initial symptoms. Characteristics are – (i) Usually appears while there is still fever. (ii) Maximum at onset. (iii) Distribution often asymmetrical. (iv) Usually begins within 1 to 5 days after onset of illness, progresses for 1 to 3 days, remains stationary for about a week and then shows rapid improvement for some weeks and then slower. (v) Absence of sensory loss.

Distribution of Paralysis

Usually patchy, may produce monoplegia, paraplegia or quadriplegia.

(a) *Lower limbs* – more frequently affected. Usually quadriceps, tibialis anterior and peroneal group.

(b) *Upper limbs* – most commonly deltoid.

(c) *Trunk* – abdominal muscles, muscles of back, intercostals or diaphragm.

(d) *Respiratory disturbances* – due to paralysis of diaphragm and intercostal muscles, or affection of respiratory centre in bulbar type – anxiety, increasing weakness of voice, cough, sucking of epigastric or intercostal spaces with increasing use of accessory muscles of respiration, diminution in the numbers a patient can count after one inspiration, and cyanosis.

4. **Convalescence** – Initial paralysis usually diminishes to some extent after two or more weeks, and improvement may continue for several months. The affected muscles become flaccid whilst contraction will tend to produce severe deformities unless these are prevented. When chronic stage is reached six months to a year after initial infection, no further spontaneous improvement can be expected.

Clinical Types

Infection of a susceptible individual may result in one of 3 clinical manifestations:

1. **Inapparent infection** – in majority of cases. Does not progress beyond involvement of regional lymphnodes. However, replication of virus in lymphoid tissue stimulates the immune system.
2. **Abortive illness** – occurs in 4–8% cases. Infection reaches viraemic phase and foreign protein from virus is released into blood stream, as also endogenous pyrogens and other toxins from necrotic cells. This results in:

   (a) *Abortive poliomyelitis* – Presumptive diagnosis during epidemic. Brief influenza-like illness with one or more of the following symptoms – malaise, anorexia, nausea, vomiting, headache, sore throat, constipation and localized abdominal pain. Fever seldom more than 103°F. Coryza and cough uncommon.

   (b) *Non-paralytic poliomyelitis* – Subjective symptoms as in abortive type but headache, nausea, vomiting more intense, and soreness and stiffness of posterior muscles of neck, trunk and limbs. Fleeting paralysis of bladder not uncommon.

3. **Paralytic poliomyelitis**

   (a) *Spinal form* – Paralysis of flaccid type usually asymmetrical and scattered in distribution, though more severe in one extremity. Legs most frequently involved. Respiratory paralysis may result from involvement of diaphragm and intercostal muscles. Transient bladder involvement in some.

   IM injections increase the risk of paralysis in the involved limb(s).

   (b) *Bulbar form* – Muscles supplied by bulbar nuclei involved alone or with spinal musculature. Facial, palatal and sometimes pharyngeal paralysis causes change in voice, difficulty in swallowing, nasal regurgitation and choking when attempting to drink. Respiratory paralysis is the usual cause of death. Tonsillectomy predisposes to bulbar poliomyelitis.

Postpollo Syndrome - presents as a new onset of weakness, fatigue, fasciculations and pain with additional atrophy of the muscle group involved during the initial paralytic disease 20–40 years earlier. More common among women and with increasing time after acute disease. Onset - usually insidious and weakness occasionally extends to muscles that were not involved during the initial illness. Prognosis - generally good; progression is usually slow, with plateau periods of 1–10 years. Thought to be due to progressive dysfunction and loss of motor neurons that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection.

Diagnosis

1. *CSF* – Increased white cell count (usually below 500/mm^3), often with high polymorph count in first few days followed by predominance of lymphocytes. Sugar normal.

2. *Isolation of virus* – from nasopharyngeal swabs during the first 5 days of illness only, but from stools and rectal swabs containing faecal material up to 5 weeks after onset.
3. *Serology* – A fourfold rise in level of antibody to the strain of virus isolated.

Management

1. ***Preparalytic stage*** – (i) *Rest in bed* – on a firm mattress with as little disturbance of patient as possible. A padded footboard serves to protect the legs from pressure of bed-clothes and keep ankles flexed at 90°. (ii) Analgesics – for pain relief. (iii) *Heat* – in form of moist (but not wet) packs of value in relieving muscle soreness or spasm. These should be applied to painful areas for an hour or two, morning and afternoon.
2. ***Paralytic stage*** – (a) *Splints* – Paralysis of muscles which results in stretching or malposition may require application of removable splints. (b) *High fluid intake* – Particularly in patients who need to be catheterized, as secondary infection and calcium phosphate calculi are common. (c) *Physiotherapy* – when muscle tenderness has subsided, gentle massage, together with active and passive movements for purpose of relaxing the muscles and preventing contractures. These procedures should not be carried out to the point where they produce pain or fatigue. (d) *Catheterization* –may be necessary for few days. (e) *Enemas* – if abdominal muscles are weak.

   Paralysis of respiratory muscles or bulbar involvement – Use of assisted ventilation if normal acts like speaking make patient breathless, if cough is ineffective, if he cannot count up to 20 after deep inspiration, if chest excursions are feeble or he cannot push out his upper abdomen. Tracheostomy may be needed when air passages are occluded by mucus or spasm of laryngeal muscles, or may be done as a routine procedure. IV fluids. Use of assisted ventilation should be continued in bulbar cases until respiratory centres have recovered. Antibiotics to prevent pulmonary complications.
3. ***Convalescent stage*** – Physiotherapy, muscle re-education, application of appropriate corrective appliances and orthopaedic surgery. Rehabilitation of the severely paralysed patient.

Prevention

ACTIVE IMMUNIZATION – Two types of polio vaccine are used. (1) *Inactivated polio vaccine* (IPV) administered by s.c. or i.m. injection. (2) *Live attenuated oral vaccine (OPV)*. IPV is used in pregnancy, immunosuppressed and for those over age of 50 receiving vaccine for the first time because of risk of vaccine-associated paralysis with live vaccine.

Vaccination is normally given in three doses 1 month apart, to infants from 2 months of age. OPV is more practical for mass vaccination, and is more widely used. However occasionally cases of vaccine-associated paralytic poliomyelitis caused by neurovirulent revertant OPV virus have occurred in vaccinees and unvaccinated contacts. In some countries IPV/OPV schedules are being used.

Contraindications to vaccine – (1) *Breastfeeding*. It is recommended that breastfeeding be stopped 30 minutes before polio immunization, until 2 hours afterwards. This is because several antiviral substances present in breast milk interfere with replication of viruses, including poliovirus. (2) *Intercurrent infections* – such as gastroenteritis. (3) *Pregnancy* – Polio immunization should be delayed until after pregnancy unless immediate protection is required. (4) *Immunosuppressed individuals* – should receive IPV instead of OPV.

PASSIVE IMMUNIZATION – with 5-15 mL according to age of child, of gamma globulin. Some measure of protection is afforded for 6 weeks. *Indications* – Newborn in hospital who are exposed to infection, unimmunized children in hospital ward in which a case of poliomyelitis develops, nurses and medical students who have not been immunized and who have come in contact with early cases of polio.

Aseptic meningitis – Enteroviral meningitis is usually benign, though encephalitis or meningoencephalitis occurs in a few cases. Patients with gammaglobulin deficiency are susceptible to chronic meningoencephalitis. Neonates with perinatal infection are also highly susceptible, and may present with generalized sepsis. Rapid diagnosis is achieved by isolating virus or detecting viral RNA in CSF and, when used in conjunction with bacterial culture results, is useful in differentiating viral from bacterial meningitis.

Acute myocarditis – Coxsackievirus B is the most common viral cause. Patients may present with a recent history of febrile illness, symptoms of heart failure or pericarditis. Evidence suggests that enterovirus may persist in the heart, leading to chronic myocarditis or dilated cardiomyopathy.

Hand, foot and mouth disease – is an ulcerative exanthema involving buccal mucosa, hands and feet. Most cases are uncomplicated, but other manifestations (e.g. meningitis) may also occur. It often occurs in epidemics, and is caused most commonly by Coxsackievirus A16 and enterovirus 71.

Type 1 diabetes – has an extended preclinical phase, and enterovirus infections may coincide with development of islet cell autoantibody responses in pre-diabetic individuals. Thus, enteroviruses may contribute to diabetogenesis at different stages.

8. TOXOPLASMOSIS

Toxoplasmosis is a zoonotic infection caused by the protozoan parasite *Toxoplasma gondii.* Worldwide, infection is most common in warm, wet countries. Incidence of infection increases with age.

Sources of infection – Sexual phase of *T. gondii* occurs in members of the cat family; only the cat's faeces (particularly those of kittens) are infectious. Oocysts sporulate 1–2 days after excretion, producing millions of infective sporocysts. In other animals and birds, cysts in the tissues are source of infection. Infection may also occur following blood transfusion or transplantation.

CLINICAL FEATURES

Acute acquired infection – Incubation period 3–21 days. Most patients have nonspecific flu-like symptoms with fever, malaise, myalgia and headache.

Lymphadenopathy, particularly of cervical lymph nodes is the most common presentation. The nodes are firm, unattached to overlying skin and initially tender. Lymphadenopathy usually lasts several months.

Retinochoroiditis – can be a result of congenital or acquired infection.

***Lungs*:** Among patients with AIDS who die of toxoplasmosis, 40–70% have involvement of the lungs and heart. Interstitial pneumonitis can develop in neonates and immunocompromised patients.

Rare manifestations are involvement of heart, muscle or skin. Toxoplasma encephalitis is seen typically in patients with AIDS and can be fatal.

***Congenital Toxoplasmosis*:** Acute infection in mothers acquiring T. gondii during pregnancy is usually asymptomatic; most such women are diagnosed via prenatal serologic screening. Infection of the placenta leads to hematogenous infection of the fetus. As gestation proceeds, the proportion of fetuses that become infected increases, but the clinical severity of the infection declines. Although infected children may initially be asymptomatic, the persistence of T. gondii can result in reactivation and clinical disease-most frequently chorioretinitis-decades later. If treated appropriately, upwards of 70% of children have normal developmental,neurologic and ophthalmologic findings at follow-up evaluations.

Reactivation of chronic infection following resolution of active infection. Toxoplasma cysts are scattered throughout the body and produce no symptoms.

Chronic infection may result from acute or reactivated infection. Symptoms are similar to those of chronic fatigue syndrome. Acute or chronic infection may become reactivated as a result of depressed immune function, and can manifest systemically or as localized ocular disease, which usually presents as retinochoroiditis.

Immunocompromise occurs as a result of disease (e.g. HIV/AIDS), treatment, (chemotherapy or radiotherapy) or organ transplantation.

INVESTIGATIONS

Laboratory – Dye test – Methylene blue is used to stain live *Toxoplasma.* Current infection is indicated by a fourfold increase in the dye test titre, increase in *Toxoplasma* specific IgG or presence of IgM. In newborns, specific IgA denotes congenital infection.

Imaging – CT and MRI – are useful in CNS toxoplasmosis because serology is often not diagnostic. Multiple bilateral contrast enhancing lesions are often found, but occasionally there is a solitary lesion. MRI is better in monitoring response to anti-*Toxoplasma* treatment.

MANAGEMENT

Indications for *anti-toxoplasma* treatment: Pregnancy, active ocular disease, infection in immunocompromised, and occasionally chronic infection.

First-line treatment – Pyrimethamine 200 mg loading dose followed by 50–75 mg/day po plus sulphadiazine 1–2 g po qds. (or dapsone) and folinic acid 15 mg/day po for 6 weeks. Clindamycin 0.6–1.2 g po qds. may be used when sulphonamide toxicity occurs. Immunocompromised patients must receive life-long treatment (usually 50% of actual dose). In pregnancy and neonates, spiramycin is alternated with first-line treatment. In ocular disease, corticosteroids. Congenitally infected neonates are treated with daily oral pyrimethamine (1 mg/kg) and sulfadiazine (100 mg/kg) with folinic acid for 1 year.

9. TETANUS AND OTHER CLOSTRIDIAL DISEASES

Tetanus is caused by a powerful neurotoxin (tetanospasmin) produced by strains of *Clostridium tetani* when introduced into the tissues that blocks the inhibitory synapses on motor neurons in CNS, resulting in unrestrained reflex spasm.

The toxin travels up local motor axons from the site of infection, causing local tetanus, and spreads through the blood stream to reach many axons and hence the CNS. Cranial nerves are usually affected because they are shorter, hence the common initial presentation is lock-jaw.

Predisposing factors – Wounds most likely to endanger tetanus are those for which treatment is delayed more than about 6 hours, those which are deep or contaminated with soil, metal, wood, calcium salts or bacteria; and those complicated by vascular damage causing necrosis of muscle. Spores of *C. tetani* occur in faeces of herbivorous animals and men. Any kind of damage to skin or mucous membranes may admit spores to underlying tissues (Table 17).

Table 17: Portals of entry of Clostridium tetani

1. Punctured or war wounds.
2. Otitis media.
3. Injections especially IM injections of quinine, or by narcotic addicts. Also vaccination.
4. Unsterile surgery including use of infected cat gut and swabs, criminal abortions, ritual circumcision, and ear piercing.
5. Bowel surgery and infarction of bowel.
6. Burns.
7. Animal bites and stings.
8. Firework injuries.
9. Intra-uterine death.
10. Unsterile division of umbilical cord.
11. Compound fractures.
12. Miscellaneous – Chronic skin ulcers, plaster sores, gangrenous limbs, eye infections, human bites, dental extractions.

GENERALIZED TETANUS

Incubation period – usually 6 to 10 days, rarely several months.

Clinical Features

Prodromal symptoms – Nonspecific such as malaise, fever, sweating, headache and irritability.

Presenting symptoms – Trismus (lock jaw) and dysphagia (often described as sore throat) due to painful rigidity of masseters and muscles of deglutition. Pain and stiffness in the neck and back.

Symptoms of established disease

(a) ***Rigidity*** – Rigidity affects the erector spinae and abdominal muscles producing exaggerated lumbar lordosis, neck retraction and abdominal rigidity.

(b) ***Muscle spasms*** – Often involve facial muscles producing the typical appearance of raised eyebrows, tightly closed eyes and drawing back of the lips to expose clenched teeth (risus sardonicus). In more severe cases painful muscle spasms also occur from time to time, either spontaneously or in response to stimuli such as loud sounds, injections, movements and attempted nasogastric intubation. Spasms of erector spinae muscles may produce opisthotonus. Pharyngeal spasms produce dysphagia, spasms of the larynx and respiratory muscles may cause asphyxiation or respiratory arrest. Paroxysmal increases in tone in all the affected muscle groups produce uncoordinated spinal convulsions, a form of diffuse spasm. Retention of urine is frequent. Tremor is not uncommon.

(c) ***Symptoms due to sympathetic overactivity*** – Patients with severe tetanus may develop cardiac arrhythmias, fluctuating BP, marked variation in pulse rate, impairment of cardiac output, peripheral vasoconstriction or vasodilatation, exaggerated pressor response to tracheal irritation, increased metabolic rate, pyrexia, excessive sweating and salivation. These symptoms are particularly severe in the elderly and in drug addicts.

Clinical Variants

1. ***Local tetanus*** – Mild form in which stiffness remains confined to the injured limb, sometimes to a single muscle. It may develop into generalized tetanus.
2. ***Ascending form*** – Local spasm of muscles in the vicinity of the wound, spread to neighbouring muscles and to limbs, head and trunk. After recovery the original muscle spasm may persist for days or weeks. May be the result of immunization.
3. ***Cephalic tetanus*** – results from injuries to head and neck and infections of the eye and orbit. One or more of the cranial nerves particularly VII nerve may be involved with spasm and apparent paralysis of the muscles which they supply, together with features of generalized tetanus. When pharyngeal muscles are involved selectively dysphagia caused by spasms may be induced by attempts to drink (hydrophobic tetanus).
4. ***Splanchnic tetanus*** – may follow abdominal or thoracic wounds or be post-operative. Spasms limited to muscles of deglutition and respiration.
5. ***Neonatal tetanus*** – due to sepsis of the umbilical stump. Typically a week-old infant presents with inability to suck because of spasm of facial and pharyngeal muscles, or with generalized convulsions. Crying

is hoarse and the face screwed up, with tightly closed eyes and wrinkled forehead. The arms are flexed and crossed with tightly clenched fists and the toes flexed. The back is very rigid. Cyanosis and apnoea accompany the more severe spasms.

Severity of Tetanus: Grading

Gr. I (mild) – Mild to moderate lockjaw, generalized spasticity, no spasms or respiratory difficulty.

Gr. II (moderate) – Well marked rigidity, brief spasms, mild dysphagia, tachypnoea (> 30–35/min).

Gr. III (severe) – Severe trismus, generalized spasticity, prolonged spasms often spontaneous, tachypnoea (> 40/min), apnoeic spells, marked dysphagia, tachycardia, increased autonomic NS disturbance.

Gr. IV (very severe) – (Gr. III features plus severe autonomic storms) – severe hypertension and tachycardia alternating with relative hypotension and bradycardia, or severe persistent hypertension or hypotension.

In assessing prognosis, the speed at which tetanus develops is important. The incubation period (time from wound to first symptom) and the period of onset (time from first symptom to first generalized spasm) are of particular significance; shorter times are associated with worse outcome. In neonatal tetanus, the younger the infant is when symptoms occur, the worse the prognosis.

Differential Diagnosis

1. *Other causes of trismus* – (a) Irritant local lesions of teeth (dental abscess, pericoronitis), throat (peritonsillar abscess), temporomandibular joint, masseter muscle and cervical lymph nodes. (b) Occasionally postvaccinial and postinfectious encephalitis, serum sickness and even poliomyelitis. It is commonly observed in patients envenomed by sea snakes.
2. *Meningitis* – Neck rigidity can occur in both tetanus and meningitis. Signs of meningeal irritation, diagnostic CSF.
3. *Rabies* – Dysphagia associated with spasms of inspiratory and pharyngeal muscles also occurs in rabies. No trismus. Relaxation of muscles inbetween paroxysms.
4. *Tetany* – Spasms start in periphery with carpopedal spasm. Usually associated with overbreathing or thyroid surgery.
5. *Drug dystonia* – Dystonic reactions to drugs such as phenothiazines and metoclopramide. Grimacing, spasmodic neck retraction and torticollis, wide opening of the mouth and eyes. Prompt response to diazepam or benztropine.
6. *Acute peritonitis* – Board-like abdominal rigidity as in tetanus, but in tetanus there is little or no tenderness.
7. *Functional muscle spasms* – Bizarre movements or posture, absence of constant rigidity of involved muscles, history of previous personality disorder.
8. *Catatonic schizophrenia* – might cause confusion in absence of background information.

Clinical course – Most deaths occur by 10th day. Spasms usually subside by end of second or third week, but residual muscle stiffness may persist for more than a month.

Complications

1. *Respiratory* – (a) Bronchopneumonia common cause of death, results from aspiration of stomach contents, blockage of airways by sticky secretions and lung collapse. (b) Asphyxia – may be due to one or both of the following – (i) Pharyngolaryngeal spasm – Sudden and unexpected stridor, respiratory distress or cyanosis in an early case of tetanus is due to spasm of muscles of upper airway. (ii) Respiratory muscle fixation – A patient without any major reflex muscle spasms may still die from complications of chest fixation in which the general hypertonicity involves pectoral muscles, intercostal muscles and muscles of the abdominal wall reducing vital capacity markedly. (c) ARDS – chiefly due to respiratory sepsis.
2. *Due to spasms* – Spasms can tear muscles and even avulse their insertions, with subsequent articular and periosteal calcification and myositis ossificans. Wedge fracture of thoracic vertebrae can also result from spasms.
3. *Complications due to tracheostomy and prolonged ventilatory support.*
4. *Multiple organ dysfunction* – In severe fulminant tetanus. Besides respiratory system, CVS (hypotension requiring inotropic support), GI system (ileus and massive bleeds), liver (rise in serum enzymes and bilirubin), renal insufficiency (rise in serum creatinine, rarely acute kidney failure).
5. *Sudden death* – from cardiovascular instability, excessive vagal tone giving rise to bradycardia and cardiac arrest, hypoxia due to prolonged laryngeal spasm or continuous seizures, hyperpyrexia, massive pulmonary embolism, heart block.

Diagnosis

Is confirmed by microbiology. A tissue sample (preferably) or a swab of the wound site is taken for Gram-staining and anaerobic culture. Cultures of C. tetani are tested for toxin production.

Prognosis

Can be assessed from:

1. *Type of infection* – Neonatal and puerperal tetanus carry a very bad prognosis.
2. *Type of patient* – Prognosis bad in elderly and drug addicts.
3. *Frequency and severity of spasms.*
4. *Incubation period* – Mortality higher if incubation period is short.
5. *Period of onset* – Interval of less than 48 hours between the first symptom (usually trismus) and the first spasm, carries double or treble the mortality.
6. *Severity of tetanus* – as described above.

Management

Aims of treatment – 1. Neutralize existing toxin before it gains access to the nervous system. 2. Reduce further production of toxin. 3. Control neuromuscular and autonomic manifestations. 4. Sustain the patient until effects of the toxin resolve.

1. ***Neutralization of unbound toxin*** – Hyperimmune human anti-tetanus immunoglobulin 1000–3000 units IM/IV as a single dose or anti-tetanus serum 10000 units IV after testing for sensitivity. Intrathecal HITG 1000–3000 units given before onset of major spasms may prevent disease progress.
2. ***Reduction of further toxin production*** – (a) *Care of the wound* – Removal of foreign material and debridement of non-viable tissue of entry wound. (b) *Antibiotic* – Benzyl penicillin 600 mg 6-hourly IM or IV, or Erythromycin 500 mg 6-hourly for 10 days to minimize risk of bacterial infection. Metronidazole can be used in patients allergic to penicillin.
3. ***Control of rigidity and tetanic seizures***

   (a) *Avoidance of provocative stimuli* –such as noise, unnecessary movement, and keeping injections to minimum.

   (b) *Sedative drugs* (Table 18)

   Note – Respiratory depression can occur when using combinations and the doses above are for single dose regimens.

   If drug treatment cannot control muscle spasm and seizure without impairing consciousness or respiration, muscle paralysis and assisted ventilation become necessary.

   (c) *Tracheostomy* undertaken early in patients whose disease is not controlled with conservative sedative regimen, because inadequate control of muscle spasms results in asphyxia and depression of swallowing reflex.

   (d) *Induced paralysis with ventilatory support* – Neuroparalytic agents pancuronium 2–4 mg bolus ½–1 hrly initially or gallamine 20–40 mL iv, the dose being so adjusted that the neuromuscular paralysis achieved allows for efficient ventilatory support (PaO_2 should be maintained > 70 mm Hg and $PaCO_2$ at 35–40 mm Hg.) When spasms abate, pancuronium or gallamine is stopped; but ventilatory support is continued till the patient is fit to be weaned.
4. ***Autonomic circulatory disturbances*** – (a) Hypotension (systolic BP < 70) – Fluids if volume depletion, if ineffective or inadvisable, dopamine iv. (b) Hypertensive spells (systolic BP > 200, diastolic > 110) – Propranolol 5–10 mg po or Labetalol or Esmolol bolus infusion. Morphine 2–5 mg as infusion may be used if shock-like state. (c) Sinus tachycardia – Verapamil 40 mg tds (d) Bradyarrhythmias – Atropine iv.
5. ***Nursing support*** – (a) ICU – Moderate and severe cases should be nursed in ICU. (b) Nutrition – Continuous drip feeding via nasogastric or nasojejunal tube.
6. ***General measures and physiotherapy*** – to prevent bed sores and complications of prolonged unconsciousness. Low molecular weight heparin s.c. 12-hourly to prevent deep vein thrombosis.

   Management according to severity of tetanus –

   Mild: Sedatives + Muscle relaxants

   Moderate: Sedatives + Muscle relaxants + tracheostomy

   Severe: Sedatives + tracheostomy + neuromuscular paralytic agents + ventilatory support

Table 18: Sedatives used in tetanus

Drug	*Daily dose*
Diazepam	20–200 mg
	p.o./p.r./i.m./i.v. continuous infusion 1–6 hrly (alternating with chlorpromazine)
Chlorpromazine	100–300 mg
	po, im or iv 6–12 hrly
Phenobarbitone	60–600 mg po 6 hrly
	(alternating with chlorpromazine) or 50–400 mg 6 hrly. im or iv (alternating with chlorpromazine)
Paraldehyde	12 mL pr or im 4–hrly
Morphine sulphate	10 mg im or iv over 10
	minutes 2–6 hrly

Prevention

1. Immunization – (a) *Active immunization* – with 1 mL tetanus toxoid to be repeated after 3 months, or 3 doses of 1 ml each at 3–4 weeks intervals. For prevention of tetanus neonatorum and puerperal tetanus the pregnant woman must be vaccinated against tetanus unless she has received a booster dose within the previous 5 years. (b) *Passive immunization* – with toxoid, immunoglobulin for all clean and minor wounds, and toxoid immunoglobulin plus antibiotic or metronidazole for infected wounds.
2. *Destruction of spores* – e.g. in operation theatres by filtered ventilation and by use of antiseptics on floors and walls. γ-irradiation or autoclaving of surgical instruments and dressings. Povidone-iodine for skin decontamination.
3. *Treatment of wounds* – Thorough cleaning, removal of foreign material and debridement of necrotic tissue. Use of antimicrobials.

OTHER CLOSTRIDIAL ASSOCIATED DISEASES

Various clostridial organisms giving rise to different diseases are listed in Table 19.

Botulism – The highly potent botulinum neurotoxin is produced in inadequately canned, cured or bottled foodstuffs contaminated with *C. botulinum*.

Botulinum toxin causes flaccid paralysis (symmetrical cranial- nerve palsies followed by bilateral descending flaccid paralysis) by blocking neuromuscular transmission. Management consists of intensive care and artificial ventilation.

Infant botulism (floppy-baby syndrome) results from growth of *C. botulinum* in infant intestine.

Wound botulism results from growth in infected wounds, and has been associated with non-iv injecting drug use (as with *C. novyi*). Commercially produced botulinum toxin is used parenterally for local muscle spasm and many other conditions.

Table 19: Various diseases caused by clostridial organisms

Disease	*Species*
Gas gangrene, myonecrosis,	C. perfringens
necrotizing fasciitis, cellulitis	C. novyi
	C. septicum
	C. sordellii
	C. histolyticum
Antibiotic associated diarrhoea,	C. difficile
pseudomembranous colitis	
Food poisoning (diarrhoea)	C. perfringens
Botulism	C. botulinum

10. LYME DISEASE

Lyme disease is caused by the tick-borne spirochete *Borrelia burgodoferi.* Erythema migrans is the early skin lesion, and is the most common clinical manifestation. The organism may spread, causing various later manifestations.

Transmission usually takes place when an infected tick (Ixodid tick) bites.

CLINICAL FEATURES

Localized (stage I) borreliosis: Erythema marginatum, a localized erythematous rash appearing 2–30 days after a bite. There may be local lymphadenopathy.

Early disseminated (stage II) borreliosis: After dissemination, the organism can affect many tissues, principally the nervous (isolated facial palsy which may be bilateral, other cranial n. lesions, lymphocytic meningitis and painful radiculoneuritis), musculoskeletal (persistent arthralgia and small joint arthritis) and cardiovascular system (conduction defects, rarely cardiomyopathy).

Chronic (stage III) borreliosis is uncommon. (a) Chronic Lyme arthritis, which in a few patients continues for months or years. (b) Chronic neurological manifestations include radiculoneuropathy, Lyme encephalopathy (uncommon), Lyme encephalomyelitis (rare). (c) Acrodermatitis chronica atrophicans – Lesions on the limbs initially violaceous, eventually becoming atrophic.

INVESTIGATIONS

Diagnosis is largely clinical.
(a) *Borrelia culture* is slow and has a low yield. (b) Borrelia DNA detection by PCR analysis is slightly more sensitive in biopsies from suspected erythema migrans. (c) *Antibody tests* are the mainstay of laboratory diagnosis.

Treatment – Amoxicillin, doxycycline and cefuroxime axetil orally. Parenteral antibiotics include benzyl penicillin, ceftriaxone and cefotaxime.

11. LEGIONNAIRES' DISEASE

A rare form of pneumonia caused by a gram-negative bacterium *Legionella pneumophilia.*

AETIOLOGY

The organism although water-borne, can infect man only if it is inhaled into the lungs. Individuals most susceptible are elderly men, particularly smokers, and those with low resistance due to immunosuppression or chronic debility.

CLINICAL FEATURES

Most characteristic are rapidly progressive asymmetrical patchy infiltrates. (a) Onset – 2–10 days after exposure with high fever, rigors, headaches and pains in muscles. (b) Breathlessness and cough common and haemoptysis in about 25%. (c) Mental confusion with neurological signs and diarrhoea and vomiting.

Laboratory features – WBC count raised, proteinuria, abnormal liver function tests, hyponatremia.

TREATMENT

Doxycycline 200 mg (IV/PO) bd for 72 hours followed by 100 mg bd, or Erythromycin 500 mg qds. po, or in severe cases 1g IV q6h with oral rifampicin 600 mg bd Ciprofloxacin 500 mg orally bd or 400 mg IV immediately, can be given instead of or in addition to rifampicin. Treatment should be continued for 3 weeks.

MISCELLANEOUS

Gram-staining – Common organisms

1. *Gram-positive cocci* – Staph. spp., Strep. spp.
2. *Gram-negative cocci* – Gonococcus, meningococcus.
3. *Gram-positive bacilli* – Clostridium spp., Bacillus spp., C. diphtheriae, Actinomyces israeli, Gardenerella vaginalis, Listeria monocytogenes.
4. *Gram-negative bacilli* – Enterobacteriaceae (E. coli, Proteus, Klebsiella, Salmonella/Shigella spp.). Pseudomonas aeruginosa. H. influenzae, Campylobacter jejuni/coli, Brucella abortus.
5. *Acid-fast bacilli* – Mycobacteria spp., Nocardia asteroides (weakly acid-fast).

Nosocomial Sources of Infection

1. Air conditioners – Aspergilli, Staphylococcus.
2. Humidifiers – Acinetobacter spp., Pseudomonas spp.
3. Water reservoirs – Legionella pneumophilia, pseudomonas spp.
4. Foods – Staphylococcus., Streptococcus.
5. Endogenous flora – Enterobacteriaceae, staphylococcus
6. Reactivation – Herpes virus, TB, mycoses.
7. Parenteral nutrition – Candida, Staphylococcus
8. Blood transfusions – (a) Hepatitis B, C, CMV. (b) Malaria, Chaga's disease, kala-azar.
9. Hydrotherapy pools – Ps. aeruginosa folliculitis.
10. Other patients and staff – Herpes viruses (esp. zoster), Listeria spp., C. difficile.

Table 20: Incubation periods of various organisms

Incubation periods	*Infection*
Short (<10 days)	Acute gastroenteritis (bacterial, viral)
	Arboviral infections, e.g. dengue, chikungunya
	Meningitis (bacterial, viral)
	Relapsing fever (Borrelia spp.)
	Respiratory tract infection (bacterial, viral including influenza)
	Rickettsial infection, e.g. tick typhus, scrub typhus
	Bacterial
	• Brucellosis
	• Enteric fever (typhoid and paratyphoid fever)
	• Leptospirosis
	• Q fever
	Fungal
	• Coccidioidomycosis
	• Histoplasmosis (can be as short as 3 days)
	Protozoal

Contd...

Incubation periods	*Infection*
	• Chaga's disease (acute)
	• Malaria (Plasmodium falciparum)
	• Trypanosoma rhodesiense
	Viral
	• CMV, EBV, HIV, viral haemorrhagic fevers
Long (>21 days)	Bacterial
	• Brucellosis
	• Tuberculosis
	Fluke
	• Schistosomiasis, acute (Katayama fever)
	Protozoal
	• Amoebic liver abscess
	• Malaria (including Plasmodium falciparum)
	• Trypanosoma gambiense
	• Visceral leishmaniasis
	Viral
	• HIV
	• Viral hepatitis (A-E)

CMV = cytomegalovirus: EBV = Epstein-Barr virus; HIV = Human immunodeficiency virus.

CHAPTER

11

Tropical Diseases

1. PROTOZOAL INFECTIONS

MALARIA

Acute febrile illness characterised by paroxysms of fever as a result of asexual reproduction of plasmodia within the red cells. *Plasmodium vivax, P. ovale* and *P. malariae* are associated with morbidity but no major mortality; *P. falciparum* and also are the parasites responsible for some potentially fatal malaria.

Transmission

Requirements for transmission of infection are (a) presence of suitable anopheline mosquito, (b) reservoir of malaria infection in the area, (c) suitable non-immune or partly immune hosts and (d) an environmental temperature with suitable humidity. (Malaria usually does not occur at altitudes of over 6,000 feet). Infection is normally transmitted to man by the bite of a mosquito, rarely it may occur across the placenta, or as a result of blood transfusion, or syringe-transmitted malaria among drug addicts.

Infection is initiated by sporozoites from the bite of a female *Anopheles mosquito.* The sporozoites multiply within hepatocytes, giving rise to thousands of merozoites, which invade RBCs. In the RBCs the small ring forms grow through the trophozoite stage to the schizont form, which ruptures and releases further merozoites.

In P. vivax infection, gametocytes are produced early in the disease, thus making for more efficient transmission than P. falciparum. Hypnozoites in the liver can cause multiple relapses. Complications regularly associated with P. vivax are thrombocytopenia, anaemia and occasionally splenic rupture.

This asexual cycle in the blood lasts 48 hours in P. falciparum, P. vivax and P. ovale infections, and 72 hours in P. malariae. The parasites often do not develop synchronously, however, and the fever associated with schizont rupture may be continuous rather than periodic, particularly in falciparum malaria.

See Figure 1 for the life cycle of malarial parasites.

Pathogenesis

Clinical symptoms and signs are caused by the asexual forms of the parasite, which invade and destroy RBCs, localise in tissues and organs by binding to endothelial cells (cytoadherence), and induce release of many pro-inflammatory cytokines [e.g. tumour necrosis factor-α (TNF-α)].

The initiating step in pathogenesis is when merozoites invade RBCs. Once inside the cell, the ring matures via the trophozoite to the schizont stage, which binds specifically to endothelial cells in post-capillary venules in organs such as the brain. Cytoadherent parasites probably cause microvascular obstruction. Cytoadherence may also localise the effect of putative parasite 'toxins', which leads to endothelial cell activation and, or damage as a result of cytokine release.

The mature parasite is also capable of 'rosetting', a process in which RBCs containing the more mature stages of parasite bind uninfected RBCs to the surface.

Clinical Features

ONSET – Lassitude, anorexia, headache, chilliness for several days before actual attack.

PAROXYSM – 3 clinical stages:

(a) *Cold stage* – Patient shivers from head to foot, his teeth chatter and he covers himself with blankets. Temperature goes on rising. The stage lasts for about half hour.

(b) *Hot stage* – Shivering abates and gives place to a feeling of intense heat, the patient throwing off the blankets. Flushed face, headache, vomiting, dry and burning skin. Temperature rises to 40°C or more. The stage lasts for 3-4 hours.

(c) *Sweating stage* – Patient breaks into profuse perspiration, and the temperature rapidly declines with feeling of relief.

Complications in severe malaria are seen as either sequestration related such as cerebral malaria or non-sequestration related in P. vivax infection such as anaemia

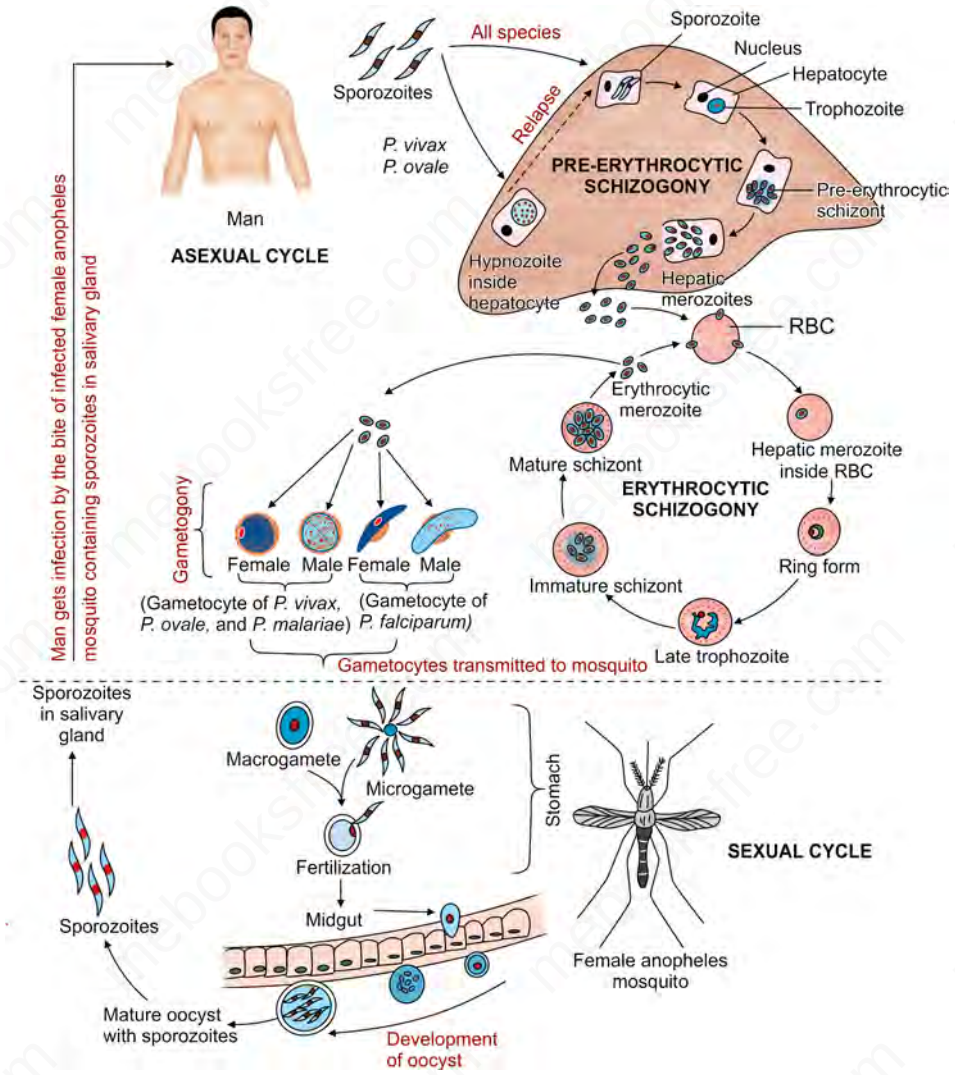


Fig. 1: Life cycle of malaria parasite

and thrombocytopenia. Severe manifestations include cerebral malaria, hepatic and kidney dysfunction, ARDS, severe anaemia, pulmonary oedema and haemoglobinuria.

Late Complications

Tropical splenomegaly syndrome (TSS) – is seen in endemic falciparum malaria. Clinical features: marked splenomegaly, lesser degree of hepatomegaly, anaemia and pancytopenia. Laboratory features – Polyclonal elevation of serum IgM levels, and high malaria antibody titres.

Quartan malarial nephropathy – is associated with P. malariae infection. Predominantly affects children between 5-8 years of age. Patient presents with nephrotic syndrome several weeks after onset of quartan fever. Disease progresses slowly to end-stage kidney failure in 3-5 years.

Manifestations of severe malaria are listed in Table 1. Lactic acidosis occurs in severe malaria due to increased anaerobic glycolysis in tissues with sequestered parasites, increased lactic acid production by parasites, decreased lactate clearance by liver and kidneys and hypotension.

Anaemia in malaria, the most common complication, is due to accelerated RBC removal by the spleen, RBC destruction at parasite schizogony and ineffective haemopoiesis.

Poor prognostic factors: Deep coma, convulsions, shock, anuria, hypoglycemia <45-50 mg/dl, platelets <50,000/mm^3, PCV <15%, bilirubin >3 mg/dl, AST and

Table 1: Manifestations of severe malaria
• Cerebral
Drowsiness progressing to coma
Repeated generalised convulsions
Retinal haemorrhages
Peripheral parasitaemia
Hyperpyrexia
• Severe anaemia
Normocytic anaemia
Hb <5 g/dl in presence of parasitaemia
• Respiratory distress
Pulmonary oedema or
ARDS
Rapid, laboured breathing
• Acute kidney failure
Urine output <400 ml in 24 hours
Serum creatinine >3 mg/dl
Macroscopic haemoglobinuria
(black water fever)
• Hypoglycemia
Whole blood glucose <40 mg/dl
• Shock (algid malaria)
Systolic BP <70 mm or
Core-skin temperature difference 10°C
• Coagulation failure
Spontaneous bleeding and/or
Laboratory evidence of DIC
• Intravascular haemolysis
Haemoglobinaemia and haemoglobinuria
• Hyper-parasitaemia >10%
Impaired consciousness of any degree
Prostration
Jaundice
Intractable vomiting
• Hepatic dysfunction
Jaundice (bilirubin >3 mg/dL) (haemolytic)
• Hypovolemia with signs of dehydration
• Acute pancreatitis (rare)
• Acidosis (pH <7.5)
• Hyperpyrexia
• Acidotic breathing
• Peripheral gangrene
• Prostration (extreme weakness without other signs)

Table 2: Causes of abdominal pain in falciparum malaria
• Acalculus cholecystitis
• Splenic rupture
• Splenic infarction
• Splenic torsion
• Hepatitis/hepatomegaly
• Acute pancreatitis

ALT > normal, parasitaemia >100000/microlitre in non-immune individuals.

Causes of abdominal pain in falciparum malaria are given in Table 2.

Diagnosis

1. *Clinical* – Periodic fever with rigour, sweating, anaemia and perhaps enlarged spleen.
2. *Blood film* – Identification of the parasites in thick and thin blood film. More likely to be found during a spike of fever. Common microscopic characters of falciparum malaria are – high concentration of parasites, predominance of thin ring-shaped trophozoites. Quantitative buffy coat analysis.
3. *Malarial antigen spot test using parasite LDH* – P. falciparum antigens, e.g. histidine-rich protein 2 (PfHRP2), LDH in blood from finger prick. These tests use monoclonal antibodies to capture the parasite antigens and are read out as coloured bands.
4. *Immunofluorescent microscopy and PCR.*

Management of Malaria

General Management

- *Admission to ICU*
- *Measurement of glucose and if possible lactate and arterial blood gases*
- *Fluid balance* – because both dehydration and overhydration can occur as a result of disease or treatment
- *Treatment of convulsions* with diazepam
- *Attention to hypoglycemia and hyponatremia*
- *Blood for cross-matching and coagulation studies*
- *Parameters for monitoring treatment* include twice daily parasite counts, regular pH and blood gas measurements and when appropriate, measurement of glucose (during iv quinine therapy), lactate, CRP and kidney function.

Table 3: Summary of pharmacotherapy for non-severe malaria in adults (adult doses given except where specified)

Indication	*Drug*	*Side effects/contraindications*
Non-severe falciparum (initial treatment): choice of three regimens	For adults: 600 mg Quinine sulphate every 8 hours for 5-7 days For children: 10 mg/kg Quinines salt every 8 hours for 7 days **+ 2nd agent as follow-on**	Mild side effects: tinnitus, hearing loss, dizziness, nausea, blurring vision Unpleasant taste Hypoglycaemia Can induce arrhythmias in context of pre-existing cardiac disease Serious cardiovascular and neurological side effects occur rarely
	Atovaquone–proguanil 4 'standard' tablets daily for 3 days. Weight <40 kg requires reduced dose	
	Artemether–lumefantrine Doses at 0, 8, 24, 36, 48 and 60 hours > 5 kg: 4 tablets per dose 25–35 kg: 3 tablets per dose 14–24 kg: 2 tablets per dose 5-14 kg: 1 tablet per dose	Use as first-line treatment for non-severe malaria in adults and children
	Arterolane 150 mg + Piperaquine phosphate 750 mg 1 tablet daily for 3 days	Avoid in early pregnancy Complete parasite clearance Good tolerability
2nd agent follow-on treatment: choice of 3 agents	Doxycycline 200 mg orally daily for 7 days	May cause gastritis, photosensitivity and complications of antibiotic use Contraindicated in pregnancy and children <12 years
	Clindamycin For adults: 450 mg every 8 hours for 7 days For children: 7-13 mg/kg/dose every 8 hours for 7 days	Choice in pregnancy and children < 12 years, but liquid formulation, difficult to obtain
	Sulfadoxine-pyrimethamine	May cause skin rashes and (rarely) Stevens-Johnson syndrome
	In children only – single dose: Up to 4 years (>5 kg) tablet 5-6 years 1 tablet 7-9 years 1 tablet 10-14 years 2 tablets 15-18 years 3 tablets	Can be taken safely whilst breastfeeding, in absence of other co-morbidities
Non-falciparum	In adults: Chloroquine 600 mg base orally followed by 300 mg at 6, 24 and 48 hours ***+ treatment for hypnozoites to prevent relapse in vivax and ovale***	
Eradicating hypnozoites (additional treatment for ovale, vivax ovale and mixed infection)	Primaquine 15 mg (ovale) or 30 mg (vivax) per day orally for 14 days Children require weight-related dosing	Contraindicated in pregnancy Screening for G6PD deficiency required prior to use as primaquine causes haemolysis in patients with G6PD deficiency and is contraindicated

Summary of pharmacotherapy for non-severe malaria in adults is given in Table 3.

Multiple drug resistance (MRD) occurs when a parasite that is resistant to one classes of drugs antimalarials develops resistance to another separate class of drugs.

Alternative oral drugs can be given when resistance is expected or patient cannot tolerate drugs such as quinine (Table 4).

Management of severe falciparum/vivax malaria is given in Table 5.

Table 4: Alternative oral drugs

Drug	*Dose*	*Comments*
Mefloquine	15 mg/kg single dose, repeated after 6 hours (usual adult dose three 250 mg tablets and further three after 6 hours)	Contraindicated in early pregnancy and in those with neuropsychiatric history. Can cause minor GI upset, abnormal sleep patterns and dreams and sometimes incoordination
Atovaquone-proguanil (Malarone)	Adult – 4 tabs/day for 3 days (Atovaquone and 100 mg proguanil)	In falciparum malaria resistant to other drugs
Artesunate/mefloquine	4 mg/kg for 3 days, plus mefloquine 15-25 mg/kg single dose on day 3	Particularly highly resistant malaria

Table 5: Management of severe falciparum/vivax malaria

Drug	*Dose*					
Quinine sulphate or dihydrochloride	20 mg/kg in 500 ml N saline infused over 4 hours 8-hrly until parasites cleared, then doxycycline or pyri-sulpha when patient can take po.					
Artesunate						
Day	**Hours**		**IV**		**IM**	
1st	0		2.4 mg/kg		2.4 mg/kg	
	After 12 hrs				1.2 mg/kg	
2nd to 7th	After q24 hrs		1.2 mg/kg		1.2 mg/kg	
Artemether based combination (ACT) ***Artemether 20 mg + Lumefantrine 120 mg***						
Body weight	**Day 1**		**Day 2**		**Day 3**	
	0 hrs	8 hrs after	Morning	Evening	Morning	Evening
5-15 kg	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
15-25 kg	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
25-35 kg	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
Adults and children >35 kg	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets
Artesunate 50 mg + Mefloquine 250 mg				Dose: One tablet bd for 3 days		
Other ACTs recommended: Artesunate + Amodiaquine Artesunate + Sulfadoxine - pyrimethamine						

Management of Specific Complications

Cerebral malaria – Antimalarial drugs. Mannitol in patients with raised intracranial pressure.

Hypoglycemia – Dextrose iv

Acute renal failure – Dialysis or haemofiltration. Non-oliguric renal failure may be managed conservatively.

Acidosis – Adequate fluid replacement. Transfusion has been shown to improve severe acidosis in anaemic young children. Early haemodiafiltration and/or ventilation may be used.

Anaemia – is mainly caused by rupture of infected cells and haemolysis. Transfusion if Hb falls below 7.5 g/dl.

Bacterial superinfection – with organisms such as Strep. pneumoniae or Salmonella spp. is common and antimicrobial drugs should be given.

Jaundice – Mild jaundice is mainly caused by haemolysis. Deeper jaundice may result from major liver involvement, but may be caused by viral hepatitis.

Hyperparasitaemia – if complicated, may be treated with exchange transfusion. Indications – (a) Parasitaemia > 30%. (b) Parasitaemia is lower but there are manifestations of severe malaria, associated medical complications (e.g. diabetes, ischaemic heart disease), patient elderly or pregnant.

Management of mixed infection – Treatment should be principally for falciparum malaria as quinine and artesunate are effective in all species. Additional treatment will later be required to eradicate dormant trophozoites if there is co-infection with vivax or ovale.

Malaria in pregnancy – In addition to increasing likelihood of severe malaria, malaria presents a significant risk to the pregnancy. Rapid therapy with an effective antimalarial is the key to good management.

Recommendations for Malaria Chemoprophylaxis

1. All pregnant women.
2. Children under 5 years of age.
3. Patients receiving corticosteroids or other immunosuppressive drugs or suffering from immune deficiency diseases.
4. Individuals homozygous for abnormal haemoglobins (e.g. SS, thalassemia).
5. Travellers to endemic areas. Prophylaxis should begin 2 weeks prior to arrival, and continued for 6 weeks after leaving.

Drugs for Malaria Chemoprophylaxis

Areas where P. falciparum is absent or chloroquine sensitive and risk of malaria is low and/or seasonal–Chloroquine phosphate 300 mg/week.

Areas with some chloroquine-resistant P. falciparum or P. vivax but with low risk of malaria

Chloroquine phosphate 300 mg/week plus
Proguanil 200 mg/day[5]

Areas with chloroquine-resistant P. falciparum or P. vivax and high risk of transmission

Mefloquine 250 mg/week
or Chloroquine 300 mg/week plus
Proguanil 200 mg/day
or Doxycycline 100 mg/day for upto maximum 8 weeks

- Should be used with caution in women who are pregnant or who might become pregnant.

LEISHMANIASIS

Leishmaniasis denotes a disease caused by genus Leishmania. There are four major clinical syndromes:

1. Visceral leishmaniasis.
2. Cutaneous leishmaniasis
3. Mucocutaneous leishmaniasis.
4. Post-kala-azar dermal leishmaniasis.

VISCERAL LEISHMANIASIS (KALA-AZAR)

Kala-azar is a disease caused by the protozoal parasite *Leishmania donovani*. The disease manifestations are many and varied, but in general it is characterised by chronicity, irregular fever, enlargement of liver and spleen, anaemia and leucopenia.

Transmission

L. donovani is transmitted by female sand-flies of the genera *Phlebotomus* and *Lutzomyia* from infected animals to humans. Other possible modes of transmission are transfusion, sexual contact, salivary and nasal secretions (when mucosae are involved) and very rarely congenital transmission. See Figure 2 for the life cycle of *Leishmania donovani.*

Pathogenesis

The inability of Leishmania-infected macrophages (in which amastigotes Leishman-Donovan bodies survive and reproduce) to produce nitric oxide appears to allow the parasite to multiply. Macrophages and dendritic cells present Leishmania antigens to T cells, which result in either an effective cellular (Th1 pattern), or an ineffective humuoral (Th2 pattern) response. Each Leishmania species produces characteristic pattern of disease, but host cellular immunity determines whether the disease is clinical or subclinical, whether the site of infection is visceral, cutaneous or mucocutaneous, whether lesions are few or diffuse, and whether response to treatment is complete or partial.

Clinical Features

Incubation period – between 2 and 6 months.

Onset – Endemic VL mainly affects children and is of gradual onset.

Symptoms

Abdominal pain – Discomfort and pain especially in left hypochondrium.

Other symptoms – Headache, malaise, cough, epistaxis, loss of weight and diarrhoea.

Signs

General appearance – Emaciated with pallor, protuberant abdomen, legs thin with sometimes oedema of feet.

Fever and toxaemia – may be the only physical signs in early cases. No characteristic form of pyrexia except double rise remittent or intermittent, lasts 2-6 weeks followed by apyrexia. A prominent feature is patients retain their appetite and are active Inspite of fever.

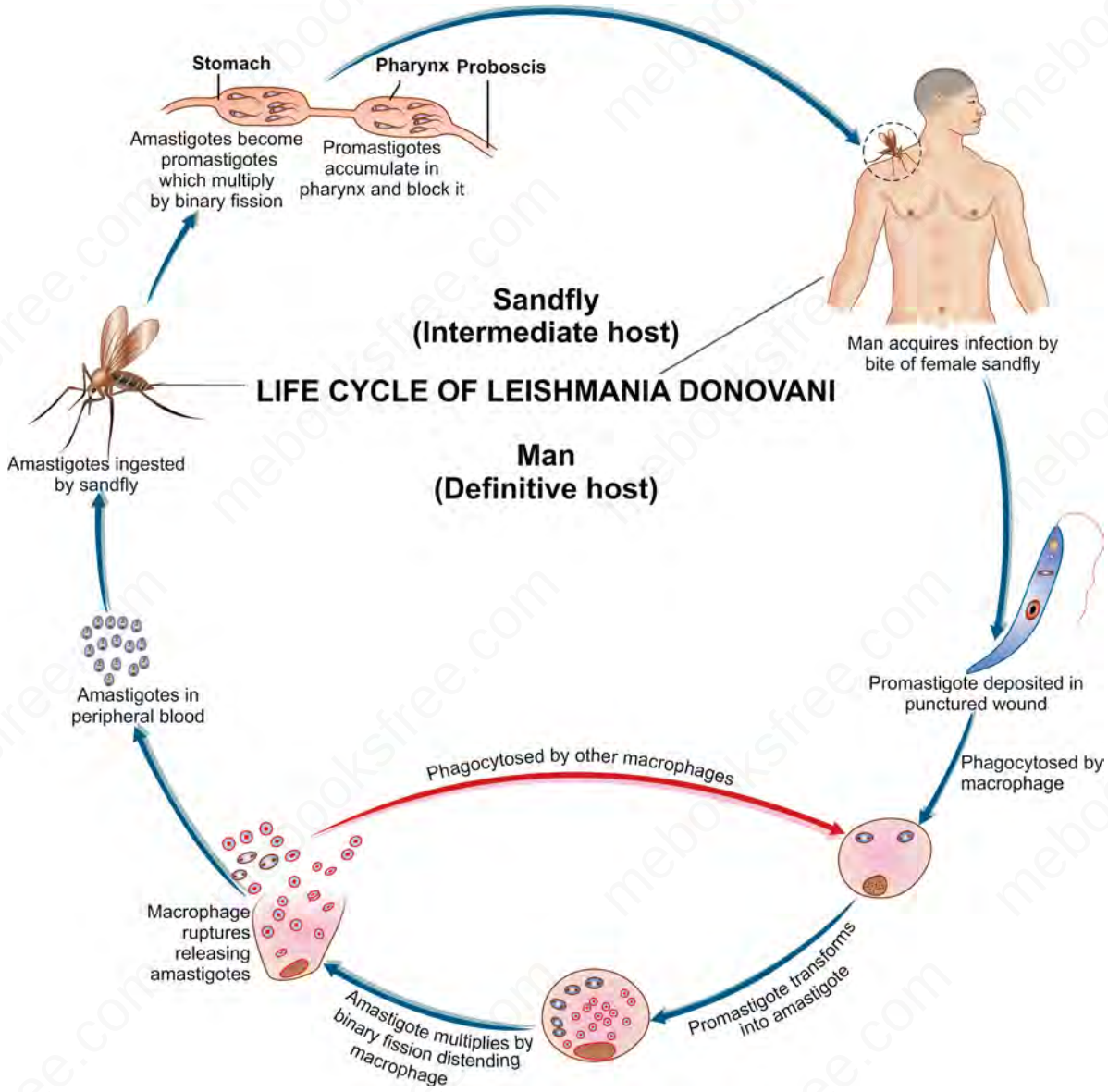


Fig. 2: Life cycle of *Leishmania donovani*

Pigmentation of skin – around malar bones and temples and around the mouth (hence labelled black sickness). Hair becomes dry, thin, brittle.

Splenomegaly – Firm, non-tender, may be massively enlarged.

Hepatomegaly – Moderate, neither painful nor tender.

Lymphadenopathy – Mainly nodes in the groin are slightly enlarged.

Jaundice – occasional.

Haemorrhagic manifestations – Epistaxis seen often, haemorrhages of skin, mucous membranes and retina rare.

Complications – Intercurrent infections especially of GI and respiratory tract (including pulmonary tuberculosis), uncontrolled bleeding.

Diagnosis

Parasitological diagnosis – In visceral leishmaniasis, demonstration of amastigotes in smears of tissue aspirates is the gold standard for the diagnosis, positive yields are aspirates from spleen, bone marrow or liver, lymphnode (Fig. 3). Buffy coat of blood (in HIV-positive patients). Culture can aid further to above yields. Leishmania can be isolated from skin in cutaneous leishmaniasis and PKDS

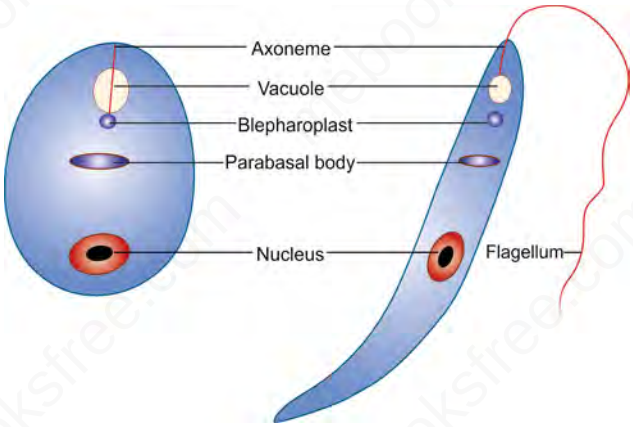


Fig. 3: Morphology of Leishmania donovani. (A) Amastigote (LD body); (B) Promastigote

or mucosal lesions in mucocutaneous disease. Slit-skin smears are taken from the raised edge of cutaneous leishmaniasis ulcers, or the centre of the nodule.

Immunological diagnosis – Direct agglutination test (DAT). Because of the difficulties associated with parasite detection, DAT based on agglutination of trypsinised whole promastigotes has been found to be highly specific and sensitive. ELISA has been used as a serodiagnostic test but its specificity depends on the antigen used. An amastigote-specific recombinant 39 amino antigen (rk39) derived from L. chagasi has been shown to be specific for antibodies in patients with VL caused by members of the L. donovani complex. A ready-to-use immuno-chromatographic strip test has been developed as a rapid test for use in field conditions. The limitation of rk39 test is that it can remain positive several years after cure and so cannot be used to detect relapse or reinfection.

Management

First-line Agents

Pentavalent antimonials – Sodium stibogluconate or meglumine antimoniate are effective in a daily dose of 20 mg/kg iv or im. Maximum tolerated dose is 30 mg/kg/day. A 28-day course in visceral and early mucocutaneous leishmaniasis, 20 days in uncomplicated cutaneous disease, and a variable duration in PKDL. Children tolerate these drugs better than adults. Full blood count, biochemistry and ECG are required.

Side effects – Increased serum amylase and liver enzymes, arthralgia and myalgia, thrombocytopenia, leucopenia, anorexia and thrombophlebitis. Pancreatitis is common. Patients complain of headache, lethargy, nausea, vomiting, a metallic taste in the mouth and pruritus. ECG shows ST segment and T wave changes. If QT is prolonged to more than 0.5 seconds, may herald ventricular arrhythmia and sudden death, therapy should be stopped for 1-2 days and the dose then reduced.

Amphotericin B – is a first line drug if resistance to antimonials. Dose: 20 doses of 1 mg/kg on alternate days.

Lipid-associated amphotericin B – Three compounds have lower toxicity than amphotericin B. (a) Liposomal amphotericin B is used for visceral leishmaniasis, is rapidly effective and non-toxic. Total dose 20-30 mg/kg in five or more daily dose of 3-4 mg/kg over 10-21 days. (b) Amphotericin B lipid complex in doses of 2 mg/kg/day for 7-10 days. (c) Amphotericin B lipid complex i.v. doses of 3 mg/kg on alternate days.

Second-line Drugs

Miltefosine 100 mg/day or 50 mg bd for 3-4 weeks or Sitamaquine or Kalozoquine 1 mg/day po for 2 weeks. Interferon α – improves cure rates with pentavalent antimonials in relapsed or unresponsive patients.

Leishmaniasis in HIV-infected patients – Symptoms may be vague, laboratory abnormalities less severe, and hepatosplenomegaly may be absent or slight. Amastigotes may be found in bone marrow aspirates or skin biopsies of febrile HIV-positive patients. GI symptoms may predominate, and amastigotes of Leishmania can be found in rectal or duodenal biopsies. About 80% of patients respond to antileishmanial treatment but most relapse 2-12 months later.

Cutaneous leishmaniasis – Here amastigotes multiply in dermal macrophages near the sand-fly bite, typically on cheeks, ears or limbs, lesions may be nodular or ulcerative, single, or multiple satellite nodules or lymphangitic spread. Most typical lesion is a chronic 2-5 cm ulcer with indurated margins that may be covered by a fibrous crust. The ulcers are painful if large or infected. Biopsies show intense lymphoid and monocytic infiltrate with granulomas. A 'tissue paper' scar remains after healing. Because of natural healing, cutaneous leishmaniasis requires treatment only when lesions are large, multiple, disfiguring or cover a joint.

Post-kala-azar dermal leishmaniasis (PKDL) – Occurs months to years after visceral leishmaniasis. The lesions of PKDL are hypopigmented patches, nodules and plaques on face, upper chest and hands. The disease is sometimes severe with desquamation of skin and mucosae. PKDL has been described in acute visceral leishmaniasis and in patients who have been symptomless earlier or who have not been treated for the disease. Parasites are scanty or absent in biopsies.

Treatment – treated with pentavalent antimonials for 60-120 days. This prolonged course leads to noncompliance. The alternative-several courses of AmB spread over several months is expensive and unacceptable for most patients. Oral miltefosine for 12 weeks, in the usual daily doses, cures most patients. (a) Pentavalent antimony or intralesionally – About 2 ml of undiluted drug is infiltrated into the base and edges of the lesion every 2-3 days for 2-3 weeks. (b) Topical preparation – 15% Paromomycin in 12% methylbenzethonium chloride as ointment. (c) Cryosurgery – Freezing with CO_2 snow.

Paromomycin 15% in methylbenzethonium chloride b.d. for 10-30 days by topical application.

Mucocutaneous leishmaniasis – usually follows cutaneous leishmaniasis by months or years, but some with mucocutaneous leishmaniasis have active cutaneous leishmaniasis. Usually, tip of the nose or upper lip are first involved with painless induration or ulceration. It may remain static or spread slowly over months to years into nasopharynx, palate, uvula, larynx and upper airways. Biopsies show chronic inflammation with scanty amastigotes. Early lesions respond well to antimonials or amphotericin B, but relapses are common.

TRYPANOSOMIASIS

African trypanosomiasis (sleeping sickness) – is caused by the parasite *Trypanosoma brucei*. The main mode of transmission is through the bite of infected tsetse flies.

Clinical Features

Insidious Onset

Haemolymphatic stage (stage I) – About 5 days after the infective bite, a small, raised papule develops at the site and increases rapidly in size. It is surrounded by an erythematous tissue reaction with regional lymphadenopathy (trypanosomal chancre) that resolves after 2-4 weeks.

Following the multiplication at the site of inoculation, trypanosomes invade the haemo-lymphatic system. Release of cytokines during periods of increased cell lysis results in intermittent fever, chills, headache and joint pains. Hepatosplenomegaly and generalised lymphadenopathy are common. Enlargement of lymph nodes in the posterior triangle is a reliable sign - Winterbottom's sign. Other signs are a fleeting patch, rash, myxoedematous infiltration of connective tissue (puffy face syndrome).

Meningoencephalitic stage (stage II) – Cerebral involvement occurs as trypanosomes cross the blood - brain barrier. There is increasing headache, change in behaviour. Convulsions are common. Sleep abnormalities lead to a somnolent and comatose state followed by death.

Diagnosis

Detection of the parasite in chancre or lymph node aspirates, blood or CSF. Serology is useful for detection of antibodies in gambiense sleeping sickness. The card agglutination test is used for rapid screening.

Management

Stage I – (a) *Pentamidine* im 4 mg/kg daily or on alternate days for 7-10 injections. Side-effects are hypotension, shock and renal, hepatic and pancreatic dysfunction, and polyneuropathy. (b) *Suramin* by slow iv injection. Serious adverse effects are rare. Test dose 5 mg/kg on day 1. Days 3, 10, 17, 24 and 31, 20 mg/kg.

Stage II – (a) *Melarsoprol* – by slow iv injection clears trypanosomes rapidly. Dose: Day 1-10: 2.2 mg/kg. Serious side-effect is acute, often haemorrhagic coagulopathy. Simultaneous administration of prednisolone is beneficial in patients with high CSF cell counts. (b) *Eflornithine* – 100 mg/kg qds. for 14 days. Adverse effects are those as with cytotoxic drugs. (c) *Nifurtimox* – is second-line drug for Melarsoprol-refractory disease. 5 mg/kg tds for 30 days.

AMERICAN TRYPANOSOMIASIS (CHAGA'S DISEASE)

It is caused by *T. cruzi,* and usually transmitted to vertebrates by blood-sucking triatomine bugs. Also through blood transfusion and congenital.

Clinical Features

Acute phase – Local reaction at site of inoculation, often presenting as orbital oedema (Romana's sign) with local lymphadenopathy. After about 2 weeks a toxaemic phase may follow with fever, hepatosplenomegaly. Death in this phase results from cardiac involvement.

Chronic phase – Gradual development of serious complications. (a) *Heart* – Amastigotes form pseudocysts in myocardial tissue causing cardiomyopathy, arrhythmia and cardiac failure. (b) *Intestinal tract* – Dilatation of intestinal organs (mega-oesophagus, mega-colon).

Diagnosis – (a) Direct methods – for acute Chaga's disease - Demonstration of trypanosomal parasites or DNA. (b) Indirect methods – for chronic Chaga's disease Demonstration of specific antibodies.

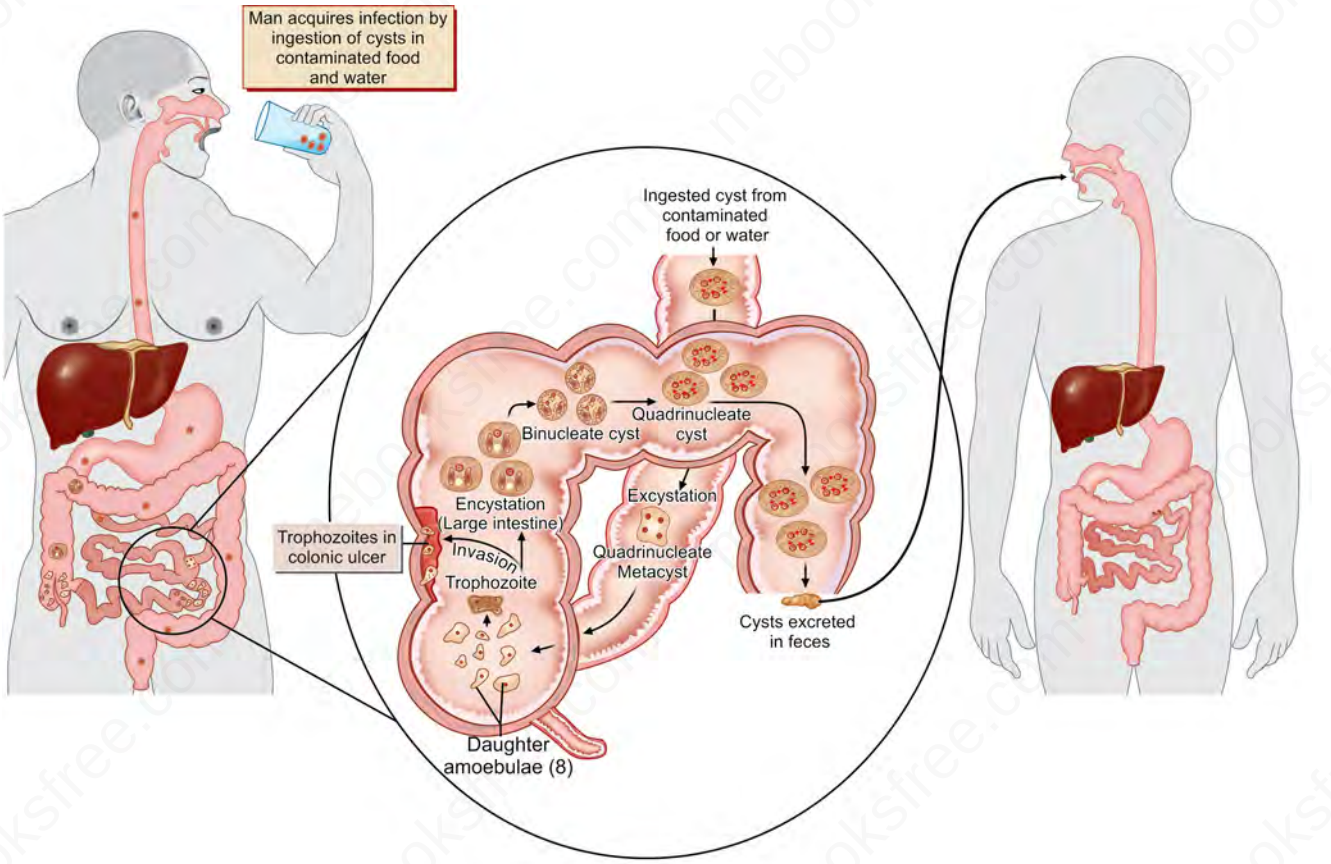


Fig. 4: Life cycle of *Entamoeba histolytica*

MANAGEMENT – (a) *Nifurtimox* 8-10 mg/kg/day in 3 divided doses for 30-120 days. (b) *Benznidazole* 5-10 mg/kg/day in 2 divided doses for 30-60 days, more effective than nifurtimox and well tolerated.

2. PROTOZOAL GI INFECTIONS

AMOEBIASIS

Amoebiasis is a common infection of the GI tract by the protozoan parasite *Entamoeba histolytica*. Although the parasite often behaves as a commensural causing no symptoms or signs (luminal amoebiasis), it can be pathogenic and result in invasive amoebiasis. This can be in the form of (a) Intestinal features (diarrhoea or dysentery). (b) Extra-intestinal lesions (usually liver abscesses) from blood-borne dissemination of amoebae.

Transmission

Infection is generally acquired by swallowing cysts of the parasite in foodstuffs faecally contaminated by unclean habits or agency of flies or use of human faeces as fertiliser, rarely contamination of water. In addition, there are high rates of infection among male homosexual populations, and epidemic outbreaks can occur in institutions such as mental hospitals and schools. See Figure 4 for the life cycle of E. histolytica.

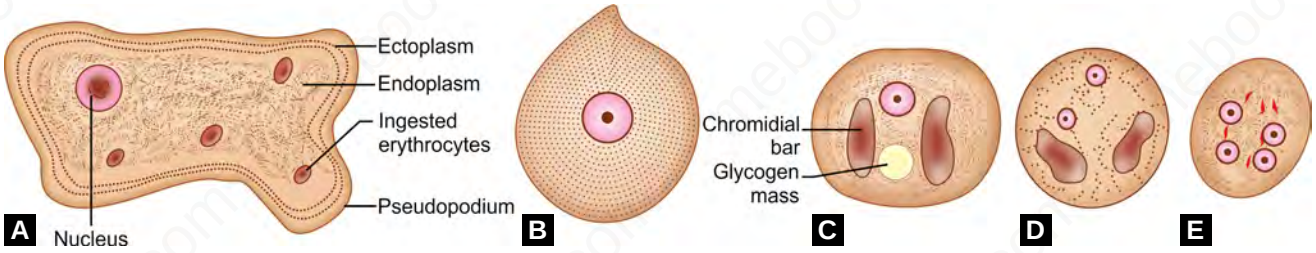
Reservoir of infection – E. histolytica is essentially a parasite of man, but is occasionally found in dogs, rats and other animals.

Intestinal Amoebiasis

1. ***Asymptomatic carriers*** – in general excrete small number of cysts. Only about 10% have GI symptoms.
2. ***Acute rectocolitis*** – usually presents as non-toxic dysenteric syndrome. Onset is gradual with loose, watery stools that rapidly become blood-stained with mucus. Tenesmus may occur.
3. ***Fulminating necrotising colitis*** (toxic megacolon) – is more common in malnourished infants, the elderly and immunocompromised patients, or after inappropriate use of corticosteroids. Features are numerous bloody

Table 6: Comparison between amoebic and bacillary dysentery

	Amoebic	*Bacillary*
Onset	Gradual	Sudden
Clinical appearance	Toxic in children, usually non-toxic in adults	Often toxic
Dehydration	Common in children, unusual in adults	Common
Tenesmus	Severe	Moderate
Hepatomegaly	Common	Uncommon
Stool	May be semiformed, blood and mucus Leucocytes uncommon	Blood and mucus, usually liquid Leucocytes common
Colonic ulcerations	Usually segmental	Diffuse



Figs. 5A to E: *Entamoeba histolytica* (A) Trophozoite; (B) Precystic stage; (C) Uninucleate cyst; (D) Binucleate cyst; (E) Mature quadrinucleate cyst

stools, generalised abdominal pain, rectal tenesmus, high fever, nausea and vomiting. Colonic perforation is a common complication. Toxic megacolon occurs occasionally and is characterised by marked abdominal distension. Diagnosis – Presence of amoebic trophozoites in stools, positive serology, leucocytosis. Abdominal radiographs may reveal a paralytic ileus located in the area of the colon if there is associated perforation. In toxic megacolon generalised distension of the colon with intramural gas may be seen.

4. ***Post-dysenteric colitis*** – (a) A milder functional form constituting the irritable bowel syndrome. (b) Ulcerative post-dysenteric colitis.
5. ***Amoeboma*** – is a late complication of previous amoebic dysentery. Clinical finding is a tender mass lesion that is usually single (often in the caecum) or occasionally multiple. It may rarely present as an intestinal occlusion simulating colonic carcinoma. Amoebae may be difficult to find in the lesion. Histology shows granulation tissue and in contrast to amoebic dysentery, amoebic serology is always positive.
6. ***Amoebic appendicitis*** – Clinical features same as that of bacterial appendicitis, but often there is also involvement of caecum, giving rise to blood-stained diarrhoea.
7. ***Amoebic typhlitis*** – Sometimes the localisation of amoebae is confined to caecum and ascending colon and clinical picture may be that of chronic typhlitis rather than acute dysentery.

Table 6 compares amoebic and bacillary dysentery.

Investigations

1. *Rectosigmoidoscopy and colonoscopy* – of benign cases show small ulcerations covered by a yellowish exudate containing many trophozoites. In more advanced cases ulcers are large and more numerous, with submucosal haemorrhages.
2. *Microscopy* – for presence of cysts and trophozoites of E. histolytica in stools or scrapings of affected mucosa (Figs. 5A to E).
3. *Serology* – Anti-amoebic antibodies are present in 75-85% of patients with invasive amoebiasis. Antigenemia is present in more than 90%, and all have IgA antibodies to cysteine-rich area of the galactose-inhibitable lectin of E. histolytica.

Extraintestinal Amoebiasis

1. ***Amoebic liver abscess*** – *Predisposing factors* – More common in adult males, excessive alcohol, malnutrition or trauma over hepatic area. History of dysentery may or may not be obtained. The abscess is usually single and the most common location is the right lobe of the liver.

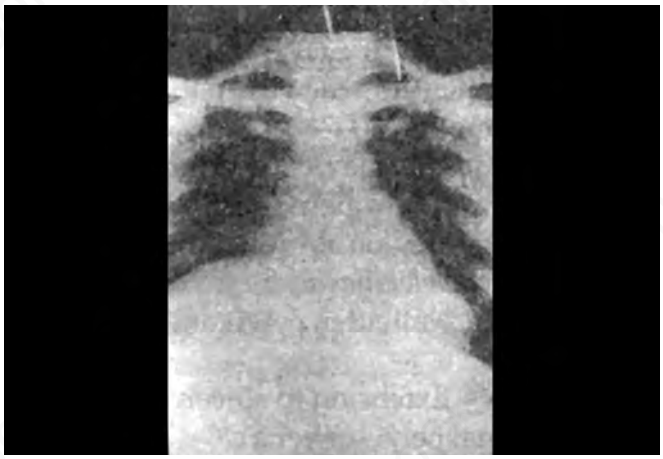


Fig. 6: Upward enlargement of liver in hepatic amoebiasis

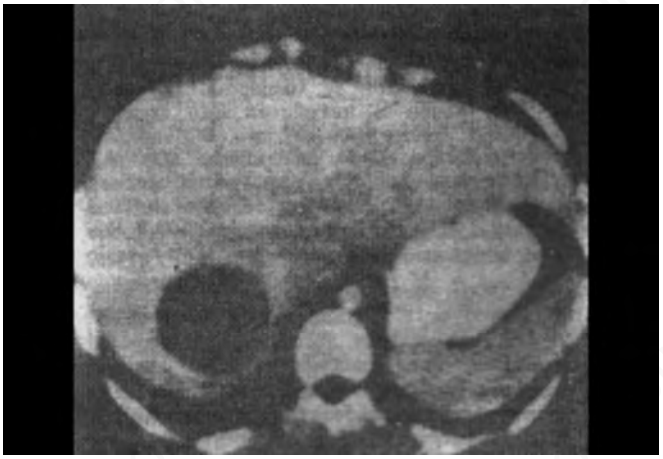


Fig. 7: CT scan of a single amoebic liver abscess

Clinical Features

Onset – insidious with no symptoms till abscess is large, or symptoms of chronic ill-health, or abrupt onset suggestive of right basal pneumonia, or sometimes acute abdomen. Rarely first noticed when abscess bursts through lung or bowel.

(a) *Pain or discomfort in liver area* – (i) At first dull and aching or sensation of heaviness in right hypochondrium, later sharp and stabbing; usually over hepatic area, rarely in epigastrium or axillary region. (ii) Pain is referred to tip of right or left shoulder when abscess is located high in one or other lobes of the liver, and there is commonly an irritant cough. (iii) Pain on firm pressure with fingertips in an intercostal space and over a limited area (compression test, point tenderness) common and valuable localising sign. Pain may be increased by deep inspiration or coughing. Patient tends to lean to the left side to relieve the pain.

(b) *Enlarged tender liver* – Localised visible bulge in epigastrium, right hypochondrium or lower intercostal spaces.

(c) *Local oedema* – of chest or abdominal wall.

(d) *Icterus* – Moderate in about 25%. Rarely deep jaundice due to obstruction by an abscess of intrahepatic bile ducts.

(e) *Abdominal tenderness* – Marked tenderness over caecum and colon if associated dysentery.

(f) *Constitutional symptoms* – (i) Fever varies between 38°C and 40°C, often in spikes, with rigours and profuse sweating in upper half of body, particularly at night. Rigours may occur and indicate threatened rupture. (ii) Profuse sweats. (iii) Emaciation. (iv) Sallow skin. (v) Rheumatic-like pains in joints.

Investigations – (a) Leucocytosis. (b) Alkaline phosphatase elevated (the most reliable biochemical indication of amoebic liver abscess). (c) CXR – Elevated right diaphragm (Fig. 6). (d) Ultrasonography or CT – Space-occupying lesion may be seen (Fig. 7). (e) Anti-amoebic serum antibodies – in more than 90%, titres reach a peak by second or third month. (f) Cellulose acetate precipitate (CAP) and immunofluorescence antibody test. CAP is usually positive in acute infection. IFAT can also reflect previous colitis infections.

Note: Stool microscopy for trophozoites or cysts is of little value because few patients have associated intestinal amoebiasis.

Different Diagnosis

(a) *Pyogenic liver abscess* – History of hepatobiliary disease, abdominal sepsis, appendicitis, diverticulitis or abdominal surgery. Jaundice, pruritus and septic shock common. Hepatomegaly and elevated diaphragm on chest radiography uncommon. Negative amoebic serology. (b) *Hepatocellular carcinoma* – when patient is febrile and wasted with vague abdominal discomfort. Distinct images on CT, and tumour markers such as α-fetoprotein or carcinoembryonic antigen are useful. (c) *Infected hydatid cyst.* (d) *Subphrenic abscess.*

Complications

Pleural effusion in more than 50%.

Extension of ALA outside the liver:

- *Brain* – Necrotising abscess-like lesion.
- *Lung* – Through anterior abdominal wall or through chest wall or through diaphragm into pleura or lung, or penetration of bronchus followed by coughing up of usually chocolate coloured material.

Table 7: Management of amoebiasis

Clinical condition	*Drug*	*Dose (Adult)*
Cyst-passers	Diloxanide furoate Iodoquinol	500 mg tds × 10 days 650 mg tds × 20 days
Amoebic dysentery or amoeboma	Metronidazole or Tinidazole or Ornidazole Secnidazole plus Nitazoxanide Diloxanide furoate Dehydroemetine	500 mg tds × 5 days 600 mg tds × 5 days 500 mg tds × 5 days 2 g single dose 500 mg bd As above 1.5 mg/kg/day × 5 im (maximum 90 mg/day)
Liver abscess	Metronidazole or Tinidazole or Secnidazole or Ornidazole	As above 500 mg iv q6h × 6-10 days 2 g od × 3 days 2 g od × 3 days 2 g od × 3 days

- *Pericardium* – A left lobe abscess may extend into pericardium.
- *Peritoneum* – May burst into peritoneum presenting as an acute abdomen.
- *Bile duct* – May press upon bile duct and manifest as obstructive jaundice.
- *Intestines* – Rarely it may work its way into the colon or duodenum when the patient may have a large loose motion.
- *Retroperitoneal* – It may extend into the posterior abdominal wall retroperitoneally with a swelling over the kidney region as presenting manifestation.
- *Skin of chest or abdominal wall* – Involvement of skin of abdominal wall after percutaneous rupture of abscess.
- *Other organs* – Extension to spleen or rupture into stomach, renal pelvis or vena cava, long bones and testis.

2. ***Pleuropulmonary amoebiasis***

Lung Abscess

Primary – Development of small bronchopneumonic areas due to embolic invasion of the pulmonary circulation by E. histolytica.

Secondary – (a) Pulmonary abscess. The liver abscess gets through adherent visceral pleura into the lung. Patient has incessant cough and brings out chocolate-coloured material for one or two days followed by blood-stained expectoration (bronchobiliary fistula). (b) Bronchohepatic fistula with pulmonary involvement. (c) Consolidation. (d) Empyema extending from liver abscess.

Bronchitis and bronchopneumonia – sometimes amounting to gangrene.

3. ***Amoebic pericarditis*** – Amoebic abscess of left lobe may rupture into pericardium and cause acute cardiac tamponade.
4. ***Cerebral*** – Abscess of brain from blood- borne infection.
5. ***Urogenital*** – Subacute cystitis and prostatitis, abscess of kidney, epididymis or testis, ovary or perianal region. Ulcer of urethra in male and cervix in female. E. histolytica may be found in urine if fistula between rectum and bladder. Amoebic vaginitis. Amoebic ulceration of glans penis.
6. ***Abscess of spleen.***
7. ***Cutaneous*** – Ulceration of skin around anus, at the site of drainage of a liver abscess, around colostomy wound in a case of chronic ulcerative colitis, or sinus of an empyema.

Management of amoebiasis is depicted in Table 7.

Management of Liver Abscess

Percutaneous aspiration of liver abscess is done with wide bored needle. Indications for liver abscess aspiration are listed in Table 8.

Site – The needle is introduced into area of maximum tenderness or into 8th or 9th intercostal spaces in midaxillary line. All available pus should be removed. If abscess is in left lobe or presenting on lower surface aspiration should be performed through the open abdomen.

Surgical drainage – performed under ultrasound or CT guidance. *Indications* – (i) Rupture of liver abscess. (ii) Imminent rupture of an inaccessible liver abscess (particularly of left lobe). (iii) When there is risk of peritoneal leakage of necrotic fluid after aspiration.

Table 8: Indications for liver abscess aspiration
• Left lobe abscess.
• Abscess is pointing.
• Massive abscess.
• Persistent localised tenderness.
• Markedly raised hemidiaphragm.
• Pleuritic pain suggesting an impending leak.
• Failure of symptoms to remit on drug therapy.
• Pyogenic or mixed infection is suspected.

Perforation – Gastric suction, IV fluids and electrolytes together with tetracycline 1 gm daily. IV metronidazole. Surgery should be avoided.

GIARDIASIS

Giardia lamblia is a micro-aerophilic, flagellate protozoan parasite of the proximal small bowel in humans, where the motile, free-living trophozoite replicates sexually and cyst formation is initiated. Many of those infected are asymptomatic cyst-excretors. Giardiasis causes diarrhoea of varying severity, and malabsorption in some patients.

Transmission

Occurs by ingestion of cysts in contaminated food and water, or through person-to-person contact in sexual activity and among children. Contaminated swimming pools can be a source of infection. Hypogammaglobulinaemia predisposes to persistent severe or relapsing giardiasis. Giardia is not an uncommon cause of diarrhoea in AIDS.

Pathogenesis

Carbohydrate-bearing lectins are involved in adhesion of trophozoites to the enterocyte brush border. The organism damages the fuzzy coat (a site of extracellular digestion) and the enterocyte surface membrane, impairing digestive functions. Giardia affects vitamin B_{12} absorption by altering intraluminal events rather than damaging the mucosa.

Clinical Features

- Diarrhoea with pale, foul smelling faeces (diarrhoea can be acute)
- Abdominal discomfort, distension and flatulence
- Marked lethargy
- Weight loss
- Symptoms regress spontaneously after several weeks, rarely they persist for months.

Investigations

- Stool microscopy after formol ethyl acetate concentration reveals cysts. Smears of fluid stools from acute onset cases may show trophozoites.
- Antigen tests.
- Jejunal fluid and biopsy sections show trophozoites.
- Barium meal – Thickening of mucosal folds and dilated loops of small bowel.
- Jejunal biopsy – Reduced villous height, increased crypt depth and increased lamina propria infiltrate of plasma cells and lymphocytes in patients with more severe symptoms and malabsorption.

Differential Diagnosis

Acute gastrointestinal infections

- Salmonella, Shigella, Campylobacter (usually associated with fever, colicky abdominal pain and often dysentery); pus cells in stools.
- E. coli and rotavirus
- Clostridium difficile infection
- Cryptosporidum (self-limiting in immuno-competent patients)
- Cyclospora cayetanensis

Persistent diarrhoea and malabsorption

- Coeliac disease (giardia may render overt previously covert coeliac disease)
- Jejunal diverticulosis
- Intestinal stricture
- Pancreatic disease

Treatment: Drugs

- Tinidazole 2 g (50-75 mg/kg) single dose, may be repeated after 7 days *or*
- Metronidazole 2 g single daily dose for 3 days, can be repeated after 7 days.

If treatment fails

- Mepacrine (quinacrine) 100 mg tds for 7 days or
- Paromomycin 500 mg tds for 10 days

Treatment during pregnancy – Metronidazole 200 mg tds for 7 days (to be avoided in the first trimester).

BALANTIDIASIS

Balantidium coli is the only ciliate that infects humans. Human infection is common only in those living in close proximity to pigs. The organism can survive outside its mammalian host as a cyst, by which the disease is transmitted.

Clinical features – The trophozoites produce an illness that clinically resembles amoebic colitis.

Treatment – Tetracycline 500 mg qds for 10 days. The organism is also sensitive to ampicillin and metronidazole.

CRYPTOSPORIDIOSIS

Clinical features – Illness varies from asymptomatic carriage to a severe, life-threatening diarrhoeal disease in HIV/AIDS patients, cryptosporidiosis is generally found in patients with low CD_4 counts.

AIDS patients may also develop a sclerosing cholangitis-like disease that presents with right upper quadrant abdominal pain and/or jaundice.

Diagnosis – Microscopy of stool smears. Faecal immunofluorescent test and faecal antigen tests.

Treatment – Paromomycin and nitazoxanide may be effective.

3. GASTROENTERITIS

BACTERIAL GASTROENTERITIS (ACUTE INFECTIOUS DIARRHOEA)

Mechanisms

Bacteria cause gastroenteritis by one of three principal processes associated with distinctive but overlapping clinical syndromes:

- Production of preformed toxins which induce vomiting and abdominal cramps within a few hours.
- Secretion of toxins after adhering to surface epithelium – Non-invasive bacteria that secrete toxins usually cause watery diarrhoea without fever.
- Invasion of intestinal mucosa causes either dysentery or enteric fever.

Bacterial causes of gastroenteritis and commonly associated clinical syndromes are listed in Table 9.

Campylobacter gastroenteritis – Infection largely occurs in children under 2 years in the developing world, and in older children and young adults elsewhere. Infection is acquired through ingestion of contaminated food or milk or close contact with infected pets.

Clinical features – Spectrum of clinical disease varies from asymptomatic carriage to life-threatening toxic megacolon. After an incubation period of 1-6 days, there is fatigue and myalgia followed by anorexia, fever, lower abdominal pains and diarrhoea. Stool samples always contain pus cells.

Complications – Guillain-Barre syndrome though rare.

Table 9: Bacterial causes of gastroenteritis and commonly associated clinical syndromes

Intoxication
Staph. aureus
Bacillus cereus
Clostridium perfringens
Watery diarrhoea
Vibrio cholera
Salmonella spp.
Enterotoxigenic E. coli
Enteropathogenic E. coli
Clostridium difficile
Listeria monocytogenes
Bacillus cereus
Dysentery
Shigella spp. (shigellosis)
Enteroinvasive E. coli
Enterohaemorrhagic E. coli
Campylobacter
Yersinia
Enteric fever
Salmonella typhi
Salmonella paratyphi

Management – Erythromycin or ciprofloxacin. Racecadotril, a potent inhibitor of enkephalinase is effective as single dose in acute infective diarrhoea in adults. Dose 1.5 mg/kg.

Shigella – Sh. infection is the classical cause of *bacillary dysentery*. Four species in decreasing order of severity of disease gives rise to dysentery are Sh. dysenteriae, Sh. flexneri, Sh. boydii and Sh. sonnei. Shigella spp. has been implicated as a cause of 'gay bowel' syndrome in homosexual men. There is no known animal reservoir (in contrast to many Salmonella spp.).

Shigella bacteraemia is uncommon except in immunocompromised host (e.g. HIV infection).

Cl. Fs. – Following an incubation period of 2-3 days, high fever, headache, malaise and anorexia occur, along with frequent small-volume stools progressing to passage of blood and pus and severe abdominal cramps, tenesmus and abdominal tenderness on palpation.

Diagnosis – Stool culture and identification of the organism by specific serological testing.

Treatment – Fluid replacement. (a) Antibiotics – Ofloxacin is drug of choice in most adults, co-trimoxazole and

Table 10: Main categories of diarrhoeagenic E. coli

Category	*Epidemiology*	*Clinical features*	*Management*
Enterohaemorrhagic E. coli 0.57:H7	Reservoir – Cattle Transmission – undercooked meat and unpasteurised milk, person-to-person	Produce bloody diarrhoea, no pus cells	Antibiotics contraindicated
Enteropathogenic	Infants <2 years. Reservoir – humans Transmission by hand and infected food	Watery diarrhoea High fatality rate Symptoms often prolonged	Cotrimoxazole in severe cases
Enteroinvasive	Reservoir – humans Transmission – person-to-person	Less severe than Shigella infection	Ciprofloxacin
Enterotoxigenic	Infants <3 years Reservoir – humans Transmission – food and water Most common cause of 'travellers', diarrhoea	Watery diarrhoea, in severe cases can mimic cholera, minimal fever	Cotrimoxazole, doxycycline or ciprofloxacin

ampicillin are alternatives in children. (b) Antidiarrhoeal agents – Single dose of Racecadotril (enkephalinase inhibitor) or Octreotide (Somatostatin analogue).

Diarrhoeagenic E. coli

Table 10 gives details about various diarrhoeagenic E. coli with epidemiological and clinical features and management.

Vibrio cholerae – The causative organism of *cholera,* is a short, curved, motile Gram-negative bacillus. The major pathogenic strain possesses a somatic antigen (01) with two biotypes – classical and El Tor. Also, a strain with somatic antigen O139, the Bengal strain has appeared.

Pathogenesis – The major factor distinguishing O1 and O139 serotypes from other 'non-cholera' vibrios is the ability to produce an enterotoxin. This consists of a ring of five 'B' subunits around a central 'A' unit. This pentameric ring structure binds to GM_1 ganglioside on the enterocyte cell membrane and the A subunit stimulates enterocyte adenylate cyclase, leading to conspicuous secretion of small intestinal fluid and ultimately diarrhoea.

Clinical features – (a) Stage of evacuation – Sudden onset with frequent loose stools, first yellow soon become colourless, watery and copious with flakes of mucus (rice water stools). Copious and incessant watery vomit. Subnormal temperature. (b) Stage of collapse – Depletion of water and salts occurs rapidly, leading to severe dehydration and hypovolemic shock, and ultimately to death.

Diagnosis – is mainly clinical. The organism can be grown from stool either directly or after alkaline enrichment.

Management – (a) Fluid and electrolyte replacement:

Mild case – Oral rehydration therapy with glucose-electrolyte solution. Constituents (g/litre):
Sodium chloride 3.5
Sodium bicarbonate 2.5
Potassium chloride 1.5
Glucose 20
Other solutions containing glucose polymers (e.g. rice water) and electrolytes are highly effective.

Severe case – IV fluids. Rate of infusion determined by skin turgor, whether eyes are sunken, pulse volume, auscultation of lung bases, measurement of urinary output.

Antibiotics – shorten duration of diarrhoea. Tetracycline 100 mg iv q6h for 24 hours, then 500 mg po for 3 days. Amoxicillin preferred in pregnant women. Doxycycline 300 mg single dose for contacts.

Immunisation – Vaccine containing suspension of 8000 organisms/ml, 0.5 ml followed after 7 days by 1 ml.

Clostridium difficile – is a Gram-positive, anaerobic spore-forming bacillus, and produces a syndrome ranging from a mild diarrhoea to pseudomembranous colitis and is often associated with antibiotic use (broad-spectrum cephalosporins). Additional risk factors are gastric acid suppression with proton pump inhibitors, enteral feeding, immunosuppressants and haemopoietic stem cell transplantation.

Clinical Features – Symptoms usually begin 4-9 days after starting antibiotic therapy to 6 weeks after finishing. Profuse watery diarrhoea, abdominal tenderness, fever and leucocytosis indicate probable colitis. The condition can progress to toxic megacolon and ultimately colonic perforation and death.

Diagnosis – 1. Toxin detection - (a) Cytotoxin assay. (b) Enzyme immunoassay. (c) PCR of stool. 2. Organism detection - (a) Common antigen testing antigen (GDH antigen). (b) Stool culture. 3. CDJ (Xperia difficile). 4. Colonic or histopathologic findings demonstrating pseudomembranous colitis.

Treatment – Stoppage of antibiotics especially clindamycin and cephalosporin. If severe colitis or if antibiotic needs to be continued, specific therapy with oral vancomycin or metronidazole. Cholestyramine and ion exchange resins which bind the toxins are alternatives.

ENTERIC FEVER

Enteric fever is usually caused by S. typhi (typhoid) or S. paratyphi (paratyphoid), and occasionally by other salmonella serotypes.

TYPHOID FEVER

Epidemiology

Causative organism – Gram-negative bacillus Salmonella typhi, a human pathogen which depends on man-to-man transfer for continued existence, and can survive for many weeks in sewage. *Transmission* – Main source of transmission in contamination of food and water with faeces from infected patients and carriers.

Pathogenesis

After ingestion and passage through gastric acid barrier, the organisms attach to small intestinal mucosa, penetrate it, and are transported by the lymphatics to the mesenteric lymph nodes. Following multiplication, they enter the blood stream via thoracic duct, then spread to bone marrow, spleen and liver, where they multiply. Secondary invasion of the blood and re-invasion of the bowel via infected bile then occurs. A particularly strong inflammatory response occurs in the ileal Payer's patches, and may lead to necrosis, ulceration, bleeding and occasionally perforation.

Incubation period – 10-15 days.

Clinical Features

Classically there is gradual onset of fever in the first week, remittent in second week and falling in third week. Patients complain of headache, anorexia, vague abdominal pain, constipation or diarrhoea, and dry cough. Rigours are uncommon. Occasional features include sore throat, epistaxis, coated tongue (typhoid V tongue), and relative bradycardia.

In the second week tender hepatomegaly, (typhoid hepatitis) and palpable spleen, and signs of bronchitis. Meningism may occur. Rose spots are scanty pink macules, usually on the trunk, that blanch on pressure are seen from second week onwards.

In the third and fourth weeks of illness gastrointestinal bleeding and intestinal perforation occur; both are life-threatening and require immediate fluid resuscitation and surgical intervention.

Untreated patients can become toxic, mentally stuporose and dehydrated, and may develop ileal perforation, GI haemorrhage, coma, shock, pneumonia, nephritis and acute psychosis.

Laboratory Diagnosis

Various tests used in laboratory diagnosis of typhoid are listed in Table 11.

Differential Diagnosis

1. *Paratyphoid fever* – (a) Mode of onset often acute and atypical. (b) Wider remissions of temperature. (c) Eruption more profuse. (d) Less toxaemia. (e) Sweating and rigours more common. (f) Intestinal complications rare.
2. *Short fever* – A fever lasting for 8 to 10 days; no associated signs, probably of viral origin. Subsides spontaneously. No complications.
3. *Amoebic liver abscess* – Pain in right hypochondrium and lower chest, moderate fever, enlarged tender liver or compression tenderness over right lower intercostal spaces. Right hemidiaphragm may be elevated and immobile on fluoroscopy.

Table 11: Laboratory diagnosis of typhoid

Test	*Comments*
Microbiological tests	
Blood culture	Gold standard test, but sensitivity may be low in endemic areas with high rates of antibiotic use
Bone marrow culture	Greater sensitivity but invasive and thus of limited clinical value
Urine culture	Variable sensitivity
Stool culture	Sensitivity lower and not used routinely
Molecular diagnostics	
PCR	Similar sensitivity to blood culture but lower specificity
Nested PCR	May replace blood culture as the new 'gold standard'
Serological diagnosis	
Widal test (tube dilution and slide agglutination)	Classic and inexpensive
	Positive by 10th day.
	Lacks sensitivity and specificity
Typhidot	Lower sensitivity than Typhidot-M
Typhidot-M	Higher sensitivity than Typhidot in some series
Tubex	Promising initial results

4. *Viral hepatitis* – in pre-icteric stage. Marked nausea and vomiting, hepatic tenderness, high coloured urine.
5. *Tuberculous meningitis* – Absence of abdominal discomfort, greater frequency of vomiting, persistence of headache after first week, irritability, irregular pupils, CSF changes.
6. *Miliary tuberculosis* – Increased respirations, irregular temperature, tachycardia, cough and cyanosis, symptoms referable to alimentary tract less pronounced. Early loss of flesh. Diagnostic CXR.
7. *Heat fever* – Not uncommon in children and aged. Fever may be continuous or touch normal for some hours every day. Absence of other physical signs. Response to lowered temperature.
8. *Subacute infective endocarditis* – (a) Fever seldom continuous or high. (b) Frequent chills with septic type of temperature. (c) Cardiac signs. (d) Anaemia. (e) Embolic phenomenon. (f) Positive blood culture.
9. *E. coli infection* – Pyelitis or septicaemia – High fever, though not of continuous type. May last for 2-3 weeks. Leucocytosis, tenderness in loins, pus in urine or positive blood culture.
10. *Malaria* – Sudden onset, wide diurnal variation, early splenic enlargement, malarial parasites in blood, response to antimalarial drugs.
11. *Kala-azar* – May have typhoid type of onset. Progressive splenic enlargement. Characteristic double rise of temperature. Good appetite. No toxaemia.
12. *T.B. peritonitis* – Slow onset, continuous fever and meteorism as in typhoid. Caseous masses palpable, negative serology.
13. *Brucellosis* – An epidemic disease of long duration, characterised by fever, continuous, remittent and intermittent in type, in most cases enlarged spleen, profuse perspiration, listlessness and almost invariably relapses, accompanied by pains of a rheumatic or neuralgic character, arthralgia or swelling of joints. Positive agglutination test.
14. *Infectious mononucleosis* – Abrupt onset with sore throat, prolonged pyrexia; the temperature at first remittent may later become intermittent. Considerable constitutional disturbance. Papular or maculopapular rash chiefly on trunk. Spleen rarely enlarged. Late glandular enlargement.
15. *Rickettsial infections* – Usually sudden onset. General malaise, headache, fever, chills, photophobia. Occasional vomiting. Eschar particularly in scrub typhus and Rocky Mountain spotted fever. Rash common.
16. *Psittacosis* – History of contact with parrots, pigeons or budgerigars. Influenza-like illness with atypical pneumonia. Rising titre of antibodies or single high titre to the complement-fixing antigen of Chlamydia group B.
17. *Collagen disease* – e.g. SLE or polyarteritis nodosa. Symptoms and signs referable to multiple organ systems. Weakness and weight loss.
18. *Tularemia* – "typhoid type" may occur in laboratory workers. Sudden onset with headache and fleeting pains; pyrexia may subside to normal or nearly so on 3rd to 6th day. Spleen not palpable. Positive agglutination of serum by F. tularensis.
19. *African trypanosomiasis* – Trypanosomal chancre. Periods of febrile illness (haemolymphatic stage) lasting for one week or more and accompanied by severe headache, general malaise, myalgia and joint pains, and progressive lymphadenopathy (especially in T brucei gambiense infection). Transitory erythematous rash (circinate erythema). Other organ lesions may develop – myocarditis, splenomegaly, hepatomegaly. Meningoencephalitis may develop during the course of infection. Diagnosis – Trypanosomes in blood or tissue fluid (Fig. 8). Immunodiagnostic tests – Indirect, fluorescence antibody test (IFAT) and ELISA. CSF in case of meningo encephalitis.
20. *Melioidosis* – with acute septicaemia. Clinical features of Gram-negative septicaemia with metastatic abscesses particularly in lungs, liver and spleen. Diagnosis – Demonstration of bipolar Gram-negative rods in films of pus or secretions. Culture – Isolation of Burkholderia pseudomallei.
21. *Opportunistic infections in AIDS* – See AIDS.

Management

Antibiotics used in treatment of enteric fever are given in Table 12.

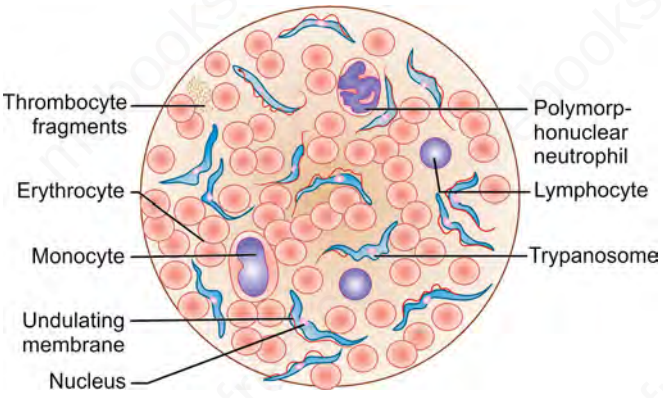


Fig. 8: *Trypanosoma rhodesience*, blood smear Giemsa stain, magn × 1100

Table 12: Antibiotics used in treatment of enteric fever

Optimal treatment				*Alternative effective treatment*		
Susceptibility	**Drug**	**Daily dose (mg/kg)**	**Course (days)**	**Drug**	**Daily dose (mg/kg)**	**Course (days)**
Uncomplicated typhoid fever						
Fully sensitive	Fluoroquinolone (such as ofloxacin or ciprofloxacin or gemifloxacin)	15	5-7*	Chloramphenicol Amoxicillin TMP-SMX	50-75 75-100 8-40	14-21 14 14
Multidrug resistance Quinolone+ resistance	Fluoroquinolone or Cefixime Azithromycin or Ceftriaxone	15 15-20 8-10 75	5-7 7-14 7 10-14	Azithromycin Cefixime Cefixime	8-10 15-20 20	7 7-14 7-14
Severe typhoid fever requiring parenteral treatment						
Fully sensitive	Fluoroquinolone (Such as ofloxacin)	15	10-14	Chloramphenicol Ampicillin	100 100	14-21 14
Multidrug resistant	Fluoroquinolone	15	10-14	TMP-SMX Ceftriaxone or	8/40 60	14 10-14
Quinolone resistant	Ceftriaxone or Cefotaxime	60 80	10-14 10-14	Cefotaxime Fluoroquinolone	80 20	10-14 14

* Three-day courses also effective, particularly so in epidemic containment.
+ Optimum treatment for quinolone resistant typhoid fever has not been determined. Azithromycin, third generation cephalosporins, or a 10-14-day course of high dose fluoroquinolone is effective. Combinations of these are now being used.

Corticosteroids – Dexamethasone 3 mg/kg stat, followed by 8 doses of 1 mg/kg 6-hourly for 48 hours, each given by IV infusion over 30 minutes, is beneficial in severely ill patients (delirious, obtunded, stuporose, comatose or shocked patients).

General care

1. Fluid and electrolyte replacement. Inotropic support in shock.
2. Diet – To provide about 3,000 calories per day. Advantages are – increases patient's resistance, haemorrhage and perforation less likely, prevents rapid emaciation. Articles of diet given – milk, lactose, toast, butter, mashed potatoes, lightly boiled egg, boiled chicken or fish, corn flour or well-boiled rice pudding, and custard, bananas and apples. Feeds 2 hourly.

Symptomatic management and management of complications

(a) *Abdominal distension* – (i) Omit sugar. (ii) Reduce amount of milk. (iii) Flatus tube.

(b) *Diarrhoea* – may be due to disease itself or sometimes the drug. (i) Reduce quantity of milk or dilute it further. Give butter-milk and sago kanji or rice kanji in water, apple juice or pomegranate juice. (ii) Omit sugar. (iii) If intractable stop milk and give albumen water or whey for few days.

(c) *Hyperpyrexia* – (i) Tepid sponge. (ii) Ice bag to head. (iii) Sponging with ice-water. (iv) Ice water enema.

(d) *Haemorrhage* – Most episodes of GI bleeding are self-limiting, and only a few patients require transfusion.

(e) *Perforation* – (i) Slow perforation – Gastric suction and IV fluids. Broad spectrum Gram-negative agent (e.g. cefotaxime with metronidazole). (ii) Acute perforation – Laparotomy.

Relapse comprises a second episode of fever, usually milder than the first, occurring 1 or 2 weeks after recovery from the episode. It is managed as in the initial episode.

Treatment of carriers – 4-week course of fluoroquinolone gives best results.

Immunisation

(a) *Anti-triple typhoid vaccine* containing in each ml. 1,000 million typhoid organisms, 250 million each of paratyphoid 'A' and 'B' organisms. Course of 3 injections of 0.5 ml, 1 ml and 1 ml subcutaneously at intervals of not less than 7 days or not more than 28 days. Immunity lasts for about 12 months. Disadvantages are: (i) The paratyphoid antigens in the vaccine are of doubtful effectiveness but also presence of extra proteins of Paratyphi organisms cause local pain, headache and

fever. (ii) Vaccination with TAB does not stimulate cell mediated immunity. (iii) Antibodies produced by TAB differ from those produced during the disease. Hence WHO has recommended that TAB should be discontinued.

(b) *V1 capsular polysaccharide typhoid vaccine* – 25 mg in each dose. Single dose (0.5 ml) SC or IM gives protection for 3 years. However, the V1 antigen does not invariably provoke V1 antibody. Booster every 2 years.

(c) *Ty21a-oral vaccine* – TY21a is a galactose epimerase mutant S. typhi given as oral enteric coated capsules. The bacilli invade mononuclear cells and undergo 4-5 cell divisions in intestinal tract. This stimulates immunity, but the bacilli do not survive within the cells, as they lack the essential enzyme UDP-galactose-4 epimerase and are therefore avirulent. The vaccine stimulates cell mediated immunity and also stimulates intestinal IgA. Dose – One capsule on days 1, 3 and 5 irrespective of age one hour before meal with milk or water. Not recommended for children under 6 years of age. Protection commences 2 weeks after last capsule and lasts for at least 3 years. Booster every 5 years. Contraindications – Immunodeficiency states including treatment with immunosuppressive and antimitotic drugs, acute febrile illness and acute intestinal infection. Adverse reactions – Mild GI disturbance, transient exanthema.

Salmonella gastroenteritis – Animals are a reservoir for human infection which usually follows consumption of food, water or milk contaminated with animal faeces. Person-to-person spread can also occur, most notably from infants and individuals with faecal incontinence. Epidemics have resulted from infected eggs involving S. enteritidis and S. typhimurium from infected beef. Treatment – Ciprofloxacin especially neonates, and immuno-suppressed patients.

Viral Gastroenteritis

Various viruses infecting the human gut are listed in Table 13.

Table 13: Various viruses infecting the human gut

Common causes of diarrhoea and vomiting
Rotaviruses
Calciviruses
Group F adenoviruses
Astroviruses
Uncommon or not common causes of diarrhoea and vomiting
Enteroviruses
Orthoreoviruses
Adenoviruses (other than group F)
Toroviruses
Coronaviruses
Parvoviruses
Causes of diarrhoea in immunodeficient patients
HIV
Cytomegalovirus
Herpes simplex virus
[Adenoviruses (type 42-47 often systemic)]

4. PLAGUE

EPIDEMIOLOGY

Causative organism – Gram negative bacilli *Yersinia pestis. Transmission* – It is normally transferred from rodent to rodent (in whom it is enzootic) by fleas (Xenopsylla cheopis). Man can be infected through the infected flea or occasionally by louse or bedbug, and sometimes from droplet infection from cases of pneumonic plague. Permanent immunity results from an attack.

Incubation period – 2-4 days.

CLINICAL FEATURES

1. ***Bubonic plague*** – commonest variety.
   (a) *Stage of invasion* – Bodyache, mental confusion. Bubo appears on second or third day, usually in groin. Very tender and associated with cellulitis of surrounding tissues.
   (b) *Febrile stage* – Onset may be with high fever without prodromata. The temperature continues as a high remittent fever for 2-5 days and then falls suddenly, or gradually after 3-4 days, synchronous with the full development of the buboes. It may rise again if and when the buboes suppurate. Congested eyes, speech dull resembling alcoholic intoxication. Marked prostration, delirium, vomiting and oliguria, retention of urine, coma and convulsions may occur. Thready pulse, dilatation of heart and perhaps haemorrhages in later stages. Spleen and liver enlarged. Death may occur on third or fifth day.
   (c) *Stage of recovery* – Constitutional symptoms abate usually on 10th day with fall of temperature and perspiration. Bubo continues to enlarge and may burst, or suppuration may not occur.

2. ***Primary pneumonic*** – Rigour, malaise, vomiting, fever, and prostration. Chest pain, dry cough, dyspnoea and cyanosis with profuse, watery, blood-tinged sputum. Haemorrhages frequent. Unilateral to begin with, later might progress to bilaterally.
3. ***Septicemic*** – Systemic dissemination via blood stream with involvement of many organs. Haematogenous invasion of lungs results in secondary pneumonic plague. It can occur prior to lymph node involvement, persons older than >40 years are at increased risk.

UNUSUAL PRESENTATIONS

Cervical bubonic plague – less common than inguinal, femoral or axillary forms.

Carbuncular plague – presents with ulcerating skin lesion.

Meningitis – may be the presenting feature and is diagnosed by isolation of Y. pestis from CSF.

LABORATORY DIAGNOSIS

1. *White cell count* – Leucocytosis with absolute predominance of neutrophils.
2. *Detection of Y. pestis* – which is easily recovered from bubo aspirates, blood or sputum on culture media such as blood agar or MacConkey's agar, where it grows aerobically *Y. pestis* is a Gram-negative bacillus with bipolar beading that gives it a 'safety-pin' appearance.
3. *Serology* – Haemagglutinating antibodies to F1 antigen appear within one week of onset of illness and specific IgM and IgG can be demonstrated by ELISA techniques.

MANAGEMENT

1. *Specific* – (a) Streptomycin 30 mg/kg/day IM in 2 divided doses for 10 days to prevent relapse. (b) Tetracycline if allergy to streptomycin. 2-4 g/day in 4 divided doses for 10 days. (c) Chloramphenicol – for patients with meningitis 25 mg/kg loading dose IV followed by 60 mg/kg in 4 divided doses and after clinical improvement continued orally for 10 days. (d) Levofloxacin 500 mg OD is also approved for treatment and prophylaxis of plague
2. *Local* – In early stages buboes painted with iodine, or glycerine and belladona, or treated with infra-red rays. Opened only when they point, allowed to drain, and dressed with antibacterial powder.
3. *General* – Good nursing. Sedatives for pain and restlessness. Pneumonic plague patients must be strictly isolated to prevent droplet infection.

Immunisation – Vaccine containing 2,000 million killed organisms per ml. 0.5 followed by 1 ml after 7-10 days. Immunity lasts for 6-12 months.

Protection of contacts – Tetracycline 500 mg 6-hourly for 7 days for close contacts of plague patients or those believed to be incubating the disease. Doxycycline 200 mg/day and levofloxacin, as mentioned above, also used for prophylaxis.

5. BRUCELLOSIS

Brucellosis is a zoonosis usually caused by Brucella melitensis, Brucella suis, or Brucella abortus (in decreasing order of virulence in man). Brucellae are small, non-motile, coccobacilli.

Various zoonotic diseases affecting humans are listed in Table 14.

EPIDEMIOLOGY

Organism – Intracellular parasite belonging to the genus Brucella.

Transmission – (a) Consumption of infected unsterilised milk, and its products. (b) Milking or tending infected animals, particularly those infected animals which have delivered or aborted. Organisms may enter the body through cuts and abrasions on the hands, conjunctivae or respiratory tract. (c) Handling carcasses or meat of infected animals in abbatoirs, butchers. Veterinarians and microbiology workers are also at risk. (d) Sexual transmission may occur in man. *Age* – Rare below age of 15, three times more common in men.

Incubation period 2-4 weeks. (7-10 days following accidental inoculation).

Table 14: Zoonoses—Diseases transmitted to humans by animals

Anthrax – Goats, sheep.
Leptospirosis – Rats.
Brucellosis – Cattle.
Salmonellosis (esp. typhimurium and enteritidis) – cattle, poultry (esp. hen's eggs).
Toxocariasis – Bite wounds (ps. multocida) – canicola fever, hydatids – Dogs.
Toxoplasmosis – Dogs.
Campylobacter enteritis, yersiniosis – Birds, poultry, pigs, dogs, cats.
Rabies – Dogs, cats, foxes, bats, etc.
Rat bite fever – Rats.

CLINICAL FEATURES

1. ***Acute brucellosis***
   (a) **Non-specific early features** – Period of ill-health for about 2 weeks with fever, headache, sweating, fatigue and joint pains precede acute onset. Profuse sweats and sacroiliac arthralgia characteristic symptoms. Lymphadenopathy, splenomegaly and hepatomegaly may occur. Acute disease lasts for 2-4 weeks.
   (b) **Localised disease**
   - *Joint involvement* – Back pain (due to sacroiliitis) or involvement of lumbar spine. Affection of weight-bearing joints such as hip or knee with swelling and tenderness due to infection of joint or reactive arthritis. Sternoclavicular, and metacarpophalangeal and costochondral joints may be involved.
   - *Cardiac involvement* – Endocarditis affecting aortic valve rare.
   - *Neurological involvement* – rare. Meningitis. Radiculitis presenting as sciatica or cauda equina syndrome. Encephalopathy, myelopathy, cranial nerve palsies, transient ischaemic episodes, vascular occlusion in brain and spinal cord and ruptured mycotic aneurysm.
   - *Miscellaneous* – Pleural effusion. Skin – Red, papular skin eruption mainly on the extremities, measles-like rash or pustular lesions. Epididymoorchitis. IgA nephropathy. Lung, liver, spleen and eye involvement.
2. ***Subacute brucellosis*** – Illness fails to resolve after 4 weeks, or exacerbations occur after this time. Muscle weakness and extreme fatigue may be mistaken for neurosis. Painful joints. Periods of good health interrupted by symptoms.
3. ***Chronic brucellosis*** – Recurring exacerbations persisting for many years. Clinical picture resembles repeated attacks of influenza. Fever uncommon. Localisation of Brucella in liver, spleen, bone marrow lead to formation of granulomata.

DIAGNOSIS

Clinical – Brucellosis should be suspected in any patient with prolonged pyrexia, musculoskeletal pains and a slightly enlarged firm spleen, especially if there is history of consumption of raw milk or milk products, or occupational exposure to infected animals.

ISOLATION OF THE ORGANISM – (a) *Blood culture* – positive in more than half the patients in acute phase of B. melitensis infection, usually by about 14 days. (b) *Culture of bone marrow aspirate, liver or lymph gland tissue culture.* (c) *Serology* – Rising titres suggest acute infection, but negative serology may be found in patients with positive blood culture. (i) Standard agglutination test – IgM antibody production is associated with acute infections. Peak titres are reached 4-6 weeks after infection. (ii) 2-mercaptoethanol test – Rising titre in acute cases. (iii) Anti-human globulin test (AHG test) – useful in chronic brucellosis when agglutination titres are negative or low, and for recurrent disease. (iv) Radioimmunoassay and enzyme-linked immunosorbent assay used for individual classes of antibodies.

IMAGING – Isotope scanning with technetium detects vertebral and peripheral joint involvement before radiological changes.

Other tests – (i) Anaemia, normochromic, normocytic. (ii) Normal leucocyte count with lymphocytosis. (iii) LFTs may be abnormal with mild elevation of aminotransferases and more marked elevation of alkaline phosphatase, suggesting presence of portal tract granuloma. (iv) CSF – Elevation of protein with lymphocytic pleocytosis.

MANAGEMENT

(a) Patient > 8 and no indication of focal disease or complications – Doxycycline 100 mg bd × 45 days + Streptomycin 1 gm IM od × first 14 days or Doxycycline + Rifampicin 900 mg (15 mg/kg/d) od × 45 days or Doxycycline 200 mg od × 6 weeks. (b) Children < 8 – Rifampicin + Cotrimoxazole (2 tabs bd) × 45 days or Rifampicin × 45 days + Gentamycin/Netilmicin 5 mg/kg/d × first 5 days. (c) Neurobrucellosis – Doxycycline + Rifampicin with or without Streptomycin/Gentamycin or Doxycycline + Cotrimoxazole with or without Rifampicin. (d) Neurologic disease requires prolonged treatment (for 3-6 months), usually with ceftriaxone supplementation. (e) Brucella endocarditis is treated with three drugs regimen aminoglycoside + tetracycline + rifampin).

Prevention – 1. Pasteurisation or boiling of milk. 2. Vaccination of female calves. 3. Slaughter of infected cattle.

MELIOIDOSIS

It is caused by Burkholderia pseudomallei, a Gram-negative bacillus found widely in soil and surface-water of

paddy and other fields. Man usually acquires infection through respiratory tract or skin. DM increases the risk manifold, clinical manifestations vary from subclinical disease to overwhelming infections, and practically every organ can be affected. *Diagnosis* – Blood culture and serology. *Treatment* – In septicemic infection, combination of cotrimoxazole, doxycycline and chloramphenicol. Other useful drugs are Ceftazidime, and imipenem.

Pinta – Non-venereal spirochaetal infection caused by Treponema carateum. Transmission by direct contagion from infectious skin lesions. Begins at inoculation site by a small papule that progresses to erythematous plaques in several months. Erythematous, squamous patches develop later, mainly on extremities, face and neck. Tertiary stage of the disease is characterised by depigmented or atrophic lesions of the skin, often of the legs with hyperkeratosis of the soles.

Treatment – Single dose of benzathine penicillin 1.5 g IM.

6. LEPROSY

A chronic infectious disease caused by *Mycobacterium leprae* with a predilection for cooler, superficial regions of the body, namely skin, mucous membrane, and peripheral nerves. Clinical manifestations depend upon the host's cellular responses to the infecting organism. Patients with low resistance develop generalised infection termed *lepromatous leprosy,* whereas those with high resistance develop *tuberculoid leprosy*, with the disease localised to skin and peripheral nerve. Intermediate forms are known as *'borderline'*.

EPIDEMIOLOGY

M. leprae, is a slowly multiplying organism which has been grown in the footpads of mice and in the armadillo.

Transmission – Lepromatous individuals discharge bacilli from the nose. Infection occurs through the nose followed by haematogenous spread to skin and nerve.

PATHOGENESIS

M. leprae has a predilection for Schwann cells and skin macrophages. The patient's immune response determines the features of the disease; the two poles are tuberculoid (paucibacillary) and lepromatous (multibacillary) leprosy. At the tuberculoid pole, cell-mediated immunity and delayed hypersensitivity control bacillary multiplication. In the lepromatous form, there is cellular anaergy towards M. leprae, resulting in abundant bacillary multiplication. Between these two is a continuum, varying from moderate cell-mediated immunity (borderline tuberculoid) through true borderline, to little cellular response (borderline lepromatous).

IMMUNOLOGY

Both T cells and macrophages are involved.

Tuberculoid leprosy – Skin tests with lepromin elicit strongly positive responses. Patients have a Th1-type response to M. leprae, producing interleukin-2 (IL-2) and interferon-g (IFNg). This strong-mediated response clears antigen, but with concomitant local tissue destruction.

Lepromatous leprosy – Skin tests with lepromin are negative. Lepromatous patients exhibit T cell failure and macrophage dysfunction, with defect in production of IL-2 and IFNg, they produce Th2-type cytokines.

Immune-mediated Reactions

Type 1 reactions are episodes of delayed hypersensitivity occurring at sites of localisation of M. leprae antigens.

Type 2 reactions – Erythema nodosum leprosum results from immune complex deposition.

Classification – Depending on immunological clinicopathological and bacteriological features, leprosy is classified into polar (stable) leprosy and borderline unstable leprosy.

- Tuberculoid leprosy (TT)
  (in patients with good immunity)
- Borderline leprosy (BT)
- Midborderline (BB)
- Borderline lepromatous (BL)
- Lepromatous leprosy (LL) (in patients with poor immunity)

Other types of leprosy are:

1. Intermediate leprosy
2. Histoid leprosy
3. Neuritic leprosy

Clinical features: According to WHO, in an endemic area, an individual should be considered as having leprosy if he/she shows one of the following cardinal signs:

- Skin lesions consistent with leprosy with definite sensory loss, with or without thickened nerves
- Skin smears positive for acid fast bacilli

- A person presenting with skin lesions or symptoms suggestive of nerve damage in whom cardinal signs are absent or doubtful should be labelled as a 'suspected case'.

SKIN LESIONS

- Can be single (TT) or multiple (LL)
- Usually hypopigmented, though may be erythematous.
- Usually macules or papules, in BL or LL papules or nodules may be seen.
- May be well defined (TT, BT), or poorly defined (BL, LL), when nodules of BL and LL subside there may be dermal atrophy.
- Absent hair and sweating are more conspicuous in TT and BT. Hence these lesions may appear dry.
- Anaesthesia/hypoanaesthesia - Anaesthetic lesions in TT, BT, BB, BL hypoaesthetic, neuroaesthetic in LL. First sensation to be affected is temperature and pain.

Thickened peripheral nerves – Peripheral nerves are vulnerable at sites where they are superficial or lie in fibro-osseous tunnels. Nerves most often involved are ulnar (elbow), median (wrist), radial cutaneous (wrist), common peroneal (knee), posterior tibial and sural (ankle), facial (crossing zygomatic arch) and great auricular (posterior triangle of neck). Affected nerves may be enlarged and tender.

Eye involvement – Blindness is a complication in patients with anaesthetic hands and feet. Eye closure is impaired when facial nerve is affected. Damage to trigeminal nerve causes anaesthesia of conjunctiva and cornea, which is then susceptible to trauma and ulceration.

Tuberculoid (TT) Leprosy

(a) *Nerve lesions* – The patient complains of sensory and/or motor symptoms depending on the type of nerve involved. Usually one single nerve is affected, or two at most.

(b) *Skin lesions* – There is one or very few skin lesions. They are large, dry, anaesthetic, sharply delineated, hairless and are hypopigmented. When they are active, they are erythematous or coppery, occurring as macular or annular lesions with thin raised rims or as plaques. The lesion is anaesthetic to touch and pinprick.

Borderline Tuberculoid Leprosy

Skin lesions more numerous, and more variable in size, shape and definition. Sensation is usually impaired. Many peripheral nerves are thickened. An acute reaction causing nerve pain or sudden weakness of hand or foot is often the presenting symptom.

Lepromatous Leprosy (LL)

(a) *Rash* – usually commences with the appearance of numerous, small, symmetrical, hypopigmented macules with normal sensation and indefinite edges, and small papules also with indefinite edges. The rash mainly affects the face, extensor surfaces of limbs and upper trunk, sparing the midline of back, axillae, groins and scalp. (b) *Thickening of nasal mucosa* – causes nasal blockage and blood-streaked discharge.

As the disease progresses, the skin, especially over the face becomes thickened and nodular (leonine facies), and ear lobes enlarge. Plaques and nodules develop; nodules may also occur on palatal mucosa, nasal septum and sclera. Eyebrows and eyelashes become scanty; lips, fingers and feet often swell. The hands become enlarged and fingers sausage-shaped or distorted by phalangeal fractures. Iritis and keratitis are common. Nasal cartilage and bones tend to be destroyed gradually (saddle-nose deformity), and laryngitis may give rise to hoarseness. Nerves of predilection steadily thicken; and destruction of the dermal nerves leads to generalised anaesthesia, which in turn leads to shortening of fingers and toes due to oft-repeated trauma. Lymph nodes enlarge and testicular atrophy leads to sterility and often gynaecomastia. Mild to moderate testicular dysfunction seen or ENL may cause orchitis.

Borderline Lepromatous Leprosy

Skin lesions are less symmetrical, and more easily seen than in lepromatous disease. Nodules are often discrete, red and succulent. Nerve damage is detectable earlier, but lesions of eye, nose, testes, muscles and bones are seldom present.

Indeterminate leprosy – Seen on face in children in endemic areas. Always a macule, ill defined, hypopigmented or slightly erythematous lesion with or without nerve thickening.

Clinical features of leprosy are summarised in Table 15.

LEPRA REACTIONS

Acute episodes in chronic course of leprosy.

(a) *Type 1 lepra reaction* – can occur in borderline leprosy and is characterised by swelling and redness of skin lesions accompanied by pain and swelling in one or more nerves. Oedema of face, hands and feet often

Table 15: Clinical features of leprosy

Clinical features	*Tuberculoid*	*Borderline*	*Borderline tuberculoid*	*Borderline lepromatous*	*Lepromatous*
Skin					
Infiltrated lesions	Defined plaques, irregular plaques, healing centres	Polymorphic partially raised edges, satellites	Papules, nodules punched-out centres	Diffuse thickening	Diffuse thickening
Macular lesions	Single, small	Several, any size	Multiple, all sizes, bizarre	Innumerable, small	Innumerable, confluent
Peripheral nerve lesions					
	Solitary, enlarged nerves	Irregular enlargement of several large nerves, asymmetrical pattern	Many nerves involved, symmetrical pattern	Late neural thickening, asymmetrical anaesthesia and paresis	Slow, symmetrical 'glove-and-stocking' anaesthesia

occur. Skin lesions may break down, and nerve damage from cellular reaction and oedema may lead to facial palsy, claw hand, or footdrop.

When type 1 lepra reactions precede initiation of appropriate antimicrobial therapy, they are termed downgrading reactions and the case becomes histologically more lepromatous; when they occur after the initiation of therapy, they are termed reversal reactions and the case becomes more tuberculoid.

(b) *Type 2 lepra reaction (Erythema nodosum leprosum)* – An antigen-antibody reaction in lepromatous leprosy. Characterised by transient erythematous nodes and patches occurring in crops in any part of the skin but particularly on face, arms and thighs, usually fading in a few days and being replaced by fresh lesions, but sometimes becoming necrotic and ulcerating. Other manifestations include fever, neuritis, swollen joints, painful tibiae, swelling and tenderness of one or more lymph glands, epistaxis, epididymoorchitis, iridocyclitis, and proteinuria. This type of reaction can be precipitated by intercurrent infection, mental and physical stress, vaccination of various types, injury, surgical operation, and by over-enthusiastic chemotherapy.

DIAGNOSIS

1. *Slit smear* stained by modified Ziehl-Neelsen method. The number of bacilli seen are estimated as the *bacillary index,* which is useful for classification. The percentage of bacilli staining homogenously – *morphological index,* is useful in assessing response to treatment.
2. *Histopathology* – Characteristic features are (a) Granuloma - (i) At the tuberculoid end of the spectrum, the granuloma is made of epithelioid cells, giant cells and lymphocytes. (ii) At the lepromatous end of the spectrum, the granuloma is ill defined and full of foamy macrophages and AFB. (b) Nerve involvement including perineural infiltrate and nerve destruction.

Lepromin test is not a diagnostic test but is of prognostic importance. If positive, it indicates good immunity to *M. leprae* and that the patient has been able to contain the infection i.e. he has tuberculoid or borderline tuberculoid leprosy.

MANAGEMENT

A. ***Chemotherapy*** - Treatment of various types of leprosy is given in Table 16.

B. ***Acute reactions*** – (a) Rest and sedatives. (b) Anti-leprosy drug should be stopped. Treatment of acute reactions in leprosy is given in Table 17.

C. ***Surgical treatment*** – (a) Excision of small lesions. Large nodules touched with strong carbolic or nitric acid. Removal of necrosed bones and splitting of nerve sheath if a nerve is constricted by dense fibrous tissue. (b) For persistent localised severe nerve trunk pain, infiltration of the thickened nerve sheath or the nerve itself with 10 ml. 1% procaine, or with the latter solution to which 25 mg of hydrocortisone and 1,500 units hyaluronidase have been added. The injection may be repeated. (c) Reconstructive surgery is required for paralysed fingers, foot-drop, and hammer toe, and plastic surgery can correct facial disfigurement caused by loss of eyebrows, facial palsy, saddle-nose deformity, ectropion, pendulous ear lobes.

Table 16: Treatment of leprosy

Type of leprosy	*Regimen*		*Treatment duration*
Paucibacillary (5 or <lesions)	Monthly supervised Rifampicin 600 mg	Daily self- administered Dapsone 100 mg	6 months
Multibacillary (>5 lesions)	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	24 months
Paucibacillary single lesion	Rifampicin 600 mg Ofloxacin 400 mg Minocycline 100 mg		Single dose

Table 17: Treatment of lepra reactions

	Type I reaction	*Type II reaction*
Mild	NSAIDs	NSAIDs
Moderate	NSAIDs	NSAIDs
	Prednisolone (10-20 mg/d)	Thalidomide (100-400 mg/d) Chloroquine Clofazimine (300 mg/d)
Severe	NSAIDs	
	Oral steroids	Thalidomide
		Oral steroids for impending nerve damage Orchitis, necrotic ENL Antimony parenteral

Note: Thalidomide is contraindicated in females in reproductive age group.

Prevention – Child contacts may be given BCG vaccination, especially infants born in leprous families. Children who have been in close contact with lepromatous leprosy can be given prophylactic dapsone for a minimum of three years. Now that quantities of M. leprae are available from experimentally infected armadillos, a specific vaccine becomes a possibility.

7. RICKETTSIAL DISEASES

SCRUB TYPHUS

Scrub typhus or tsutsugamushi disease is a febrile illness caused by bacteria of the family Rickettsiae which are small, obligate, intracellular gram negative, non-flagellate, pleomorphic coccobacilli.

Transmission – Scrub typhus is transmitted by bite of larval stage of trombiculid bites or chiggers.

Pathogenesis – Endothelial cell invasion and injury leading to increased vascular permeability, oedema, hypovolemia and ischaemia is the central physiological mechanism of all rickettsiosis. This vascular injury leads to capillary leak syndrome manifesting as multiple organ dysfunction.

Clinical features – Common symptoms include fever, maculopapular rash, headache, myalgia, dry cough and GI symptoms simulating common flu.

In scrub typhus an eschar 5 to 20 mm in diameter is formed at the site bitten by mites, and this may be considered an important finding. The site bitten by chiggers is initially a papulae followed by a blistered ulcer, and this is then covered by a black crust. Such a typical eschar is formed at the time when symptoms are manifested. It is also associated with regional lymphadenopathy. However, the characteristic eschar and rash may not always be present.

Complications – Serious complications include pneumonia, myocarditis, meningoencephalitis, acute kidney failure and GI bleeding.

Diagnosis – Specific gold standard techniques like immunofluorescence antibody test (IFA) and indirect immunoperoxidase are tests considered the tests of choice. It has the advantage of ability to detect antibodies to a number of rickettsial antigens simultaneously with the

same drop of serum and allows detection of IgG and IgM antibodies. (b) Weil Felix test – A four-fold rise in agglutinin titres in paired sera is diagnostic. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre (>1:320).

Treatment – See Table 18 for drug treatment for rickettsial fever.

Table 18: Drug treatment for rickettsial fever

Age group	*Drug/Dosage*	*Duration (days)*	*Alternate treatment*
Adult	Doxycycline 100 mg bd	12-14	Chloramphenicol Azithromycin Clarithromycin
Children	Doxycycline 4 mg/kg/day	12-14	Chloramphenicol Azithromycin Clarithromycin
Pregnancy	Azithromycin 500 mg od	12-14	Chloramphenicol Clarithromycin Rifampicin

8. RABIES

Rabies is a viral encephalomyelitis transmitted in the saliva of infected animals. Rabies is most prevalent in the canids (dogs, foxes, wolves, jackals), followed by skunks, farm animals, cats, bats and mongooses. It is uncommon in rodents, lagomorphs (rabbits, hares) and insectivores (shrews, volves, hedgehogs).

Transmission – (a) Rabies virus is transmitted when the virus is introduced into bite wounds or open cuts in the skin on to membranes. (b) Non-bite exposure – (i) Individuals exposed to aerosolised rabies virus in the laboratory. (ii) Recipients of infected cornea.

CLINICAL FEATURES

Incubation period – varies from 20 days to 90 days in majority. Varies with – (i) Age – shorter in children. (ii) Site of infection – Face about 30 days, hands 40 days, legs 60 days. (iii) Severity of wound. (iv) Animal – Shorter period in order – wolf, cat, dog.

Prodromal symptoms – Pain and irritation or discomfort at site of bite, fear and anxiety, depression, intolerance to loud sounds. Periods of irritability. Hoarseness of voice and sense of constriction in throat with difficulty in swallowing. Slight rise of temperature. Duration 1-2 days. Subsequently, symptoms of either furious or paralytic rabies develop, depending on whether the spinal cord or brain are predominantly infected.

Furious rabies – (a) *Hydrophobia* – a combination of inspiratory muscle spasm, with or without painful laryngopharyngeal spasm, associated with terror in response to attempts to drink water. Various other stimuli can excite the reaction, including a draught of cold air (aerophobia), and the sight, sound or mere mention of water. Hydrophobic spasms may end in opisthotonos and generalised convulsions with death from respiratory or cardiac arrest. (b) *Periods of excitement* – are common during which the patient becomes wild and hallucinated alternating with lucid intervals. (c) *Other features* – include meningism, cranial nerve lesions (especially III, VII, VIII), spasticity, involuntary movements, fluctuating body temperature and blood pressure, signs of autonomic over activity such as salivation, sweating and tachycardia. Priapism. Death may occur during hydrophobic spasm or patient may lapse into coma and generalised flaccid paralysis.

Paralytic rabies (dumb rabies) – is rare and seen especially in those bitten by vampire bats. Flaccid paralysis often begins in the bitten limb and ascends symmetrically or asymmetrically until it involves muscles of deglutition and respiration killing the patient in 2 or 3 days. Sensory involvement is mild and sphincter involved commonly. Hydrophobia is unusual but a few spasms may occur late in the illness.

DIAGNOSIS

Immunofluorescent testing – of skin biopsies (normally taken from the neck or face to show viral antigen in sensory nerve endings) or corneal impressions (obtained by gently abrading the cornea with a microscope slide) can establish diagnosis ante-mortem. The former is more sensitive and less damaging. Risks of brain biopsy prohibit its use as a method for diagnosis.

Viral detection – in saliva, throat swabs and tracheal aspirates is possible in 100% on days 0-4, 50% on days 5-8 and 9-12, and 14% on days 13-16. Virus isolation may take several weeks. However, PCR can establish the diagnosis rapidly when applied to saliva.

Antibody detection – is the most successful method for confirming diagnosis; however its success depends on maintaining life until antibody can be detected.

Post-mortem diagnosis – can be achieved by observation of Negri bodies in the brain, virus isolation, immunofluorescence of viral antigen in the brain, PCR and electron microscopy of brain. Negri bodies are intracytoplasmic eosinophilic inclusions; they are not pathognomonic for rabies.

MANAGEMENT

Aim is to neutralise the inoculated virus before it can enter the nervous system.

1. **Treatment of wound** – (a) Scrub with soap (or detergent) and water under a running tap for at least 5 minutes. (b) Remove foreign material. (c) Rinse with plain water. (d) Irrigate with virucidal agent, e.g. 40-70% alcohol, Povidone iodine or 0.01% aqueous iodine. (e) Explore, debride and irrigate deep wounds (if necessary, use local or general anaesthesia). Avoid suturing and occlusive dressings. (f) Consider tetanus risk and treat accordingly.
2. **Post-exposure prophylaxis** – Indications – (i) Bitten by rabid animal. (ii) The animal dies during observation and Negri bodies are found. (iii) Broken skin is soiled with the saliva of a rabid animal. (iv) Dog has disappeared or been killed without diagnosis of rabies being established and rabies is known to be present in the area. (v) Bite on face or head.

Active immunization – Human diploid cell strain vaccine (HDCSV) induces excellent antibody levels and no risk of neuroparalytic complications. *Intramuscular regimens* – 1.0 ml on days 0, 3, 7, 14, 30 and 90. Injections must be given into deltoid or anterolateral thigh in infants, not into the buttock (because antibody induction is unreliable).

Intradermal regimens

- Two-site regimen each containing one-fifth of im dose. Vaccine is given on days 0, 3 and 7, in two sites on upper arm over each deltoid. A single intradermal dose is given on day 29 and on day 90 at one site on upper arm.
- Eight-site – Injections containing 0.1 ml are given at each of eight sites over deltoid, lateral thigh, suprascapular region and lower quadrants of abdomen. On day 7, 0.1 ml is given at each of four sites over deltoids and thighs, and 0.1 ml is given at one site over deltoid, on days 28 and 90.

Side effects – (a) Local – Irritation at site of injection. (b) Systemic – Headache, fever and flu-like illness.

Passive immunisation – Administration of RIG (rabies immunoglobulin) 20 IU/kg human RIG or 40 IU/kg heterologous RIG given once, at the beginning of antirabies prophylaxis, to previously unvaccinated individuals to provide immediate antibodies until patient responds to vaccination by actively producing antibody. RIG can be given upto 7 days after administration of potent tissue culture vaccine. Beyond day 7, RIG is not indicated because an antibody response to vaccination should have occurred. RIG should be infiltrated around and into the wound even when the lesion has begun to heal. Before administrating equine RIG, hypersensitivity should be assessed by intradermal testing with a 1:10 dilution.

Indications for passive immunisation

- Exposures involving animals suspected of being rabid.
- Following unprovoked bites in endemic areas unless the animal is proved negative by laboratory examination.
- Those exposed to a rabid domestic animal, or an animal that is unavailable for examination.
- Individuals at high risk groups, including laboratory workers handling the virus (who should undergo regular antibody tests and receive booster vaccination when necessary).
- Workers in enzootic areas who may be exposed to unusual risks of infection.
- Travellers to remote areas where enzootic dog rabies is present.

SUMMARY OF POST-EXPOSURE PROPHYLAXIS

Minor exposure – including licks of the skin, scratches or abrasions, minor bites on covered areas of arms, trunks and legs:

Unprovoked attack by cat or dog available for observation.
Vaccine

Stop treatment if animal remains healthy for 10 days.

Stop treatment if animal's brain fluorescent antibody test proves negative.

Administer serum, if positive diagnosis, and complete course of vaccine.

Attack by wild animal or domestic dog or cat unavailable for observation.

Serum and vaccine.

Major exposure – including licks of mucosa or major bites (multiple on face, head, fingers or neck).

Unprovoked attack by cat or dog or attack by wild animal or domestic dog or cat unavailable for observation.
Serum and vaccine.

Stop treatment if domestic dog or cat remains healthy for 10 days.

Stop treatment if animal's brain fluorescent antibody test proves negative.

Pre-exposure prophylaxis

Indications – Those exposed to mammals before or during quarantine in kennels, zoos or laboratories, those working with rabies virus, veterinary surgeons, explorers, naturalists and speleologists travelling to rabies-endemic areas.

Vaccine – 1 ml IM or 0.1 ml intradermal on days 0, 7 and 28.

Table 19: Causes of death despite post-exposure vaccination	
1.	Inadequate wound cleaning.
2.	Delay in starting vaccine.
3.	Injections of vaccine into buttock.
4.	Lack of passive immunisation.
5.	Failure to infiltrate RIG around the wound.
6.	Use of immunosuppressive drugs, e.g. corticosteroids.
7.	Impaired immune response, e.g. cirrhosis.

Booster doses of 1 ml IM or 0.1 ml intradermal should be given every 2 years, if continued protection is needed, but laboratory personnel working with rabies virus should receive booster dose every 6 months.

Post-exposure treatment in those who have received pre-exposure vaccination – If a full pre-exposure course of HDCSV (or other established tissue culture vaccine) has been given, or if neutralising antibody, 0.5 IU or more, has been demonstrated, passive immunization with RIG is not needed. If the bite is severe or antibody titre unknown, three doses of HDCSV 1ml IM are advised on days 0, 3 and 7. If bite is not severe, only two doses on days 0 and 3. Table 19 gives causes of death despite post-exposure vaccination.

9. DENGUE

Dengue is viral infection transmitted by mosquitoes. Dengue viruses are flaviviruses related to yellow fever virus and Japanese encephalitis virus. There are four serotypes, infection with one serotype does not induce solid immunity to the others, and individuals may suffer from dengue more than once.

TRANSMISSION

Transmission is from infected to susceptible individuals by day-biting *Aedes aegypti* mosquitoes. It is not transmitted directly between humans. The virus passes from the mosquito's intestinal tract to salivary glands after an extrinsic incubation period of about 10 days. Mosquito bites after this result in infection. In the skin, dengue virus infects immature dendritic cells which mature and migrate to local or regional lymph nodes where they present viral antigen to T cells. There is also evidence of replication of DENVs in liver parenchyma cells, macrophages of lymph nodes, liver and spleen.

PATHOPHYSIOLOGY

DENVs produce several syndromes depending on age and immunological status of the host: (a) During initial infections most children have subclinical reaction or mild febrile syndromes. (b) During secondary infection, pathophysiology of the disease changes dramatically, such infections can result in acute vascular permeability syndrome leading to dengue shock syndrome (DSS). The severity of DSS is age dependent, with vascular leakage being more severe in young children. In adults, primary infection has been predominantly subclinical. Nonetheless there is a tendency for bleeding that can lead to severe haemorrhages.

Predisposing factors for life-threatening dengue infection - Individuals with asthma, diabetes and chronic diseases. Most factors include female sex, HLA class 1 alleles and AB blood group. The longer the interval between the first and second infection, the more severe is the accompanying disease. Tertiary dengue infection can cause severe disease but only rarely.

CLINICAL FEATURES

Subclinical infection may be present as undifferentiated febrile disease, often with maculopapular rash, particularly in infants and young children.

Dengue Fever (DF)

A benign febrile illness, begins abruptly with fever 5-8 days after a bite from an infected mosquito. Fever is often accompanied by severe headache, retro-orbital pain, and intense myalgia and arthralgia ('break bone fever'). A rash, macular or scarlatiniform, starts on hands and legs and then becomes generalised sparing the face. The fever usually lasts 4-7 days and is followed by complete recovery. *Complications* – are uncommon. Bleeding may occur without evidence of vascular leak. GI bleeding and menorrhagia can occur. Encephalitis or encephalopathy may occur and result in neurological sequelae.

Dengue Haemorrhagic Fever/dengue Shock Syndrome (DDS)

Pathogenesis – Pre-circulating antidengue antibody is the predominant risk factor in DHF/DSS. This may have been acquired from previous infection with a different serotype or in infants, from transplacental transfer of maternal antibody.

Table 20: WHO diagnostic criteria for DHF/DSS

Dengue haemorrhagic fever: The following all must be present
• Fever or history of acute fever
• Haemorrhagic tendencies demonstrated by at least one of the following
– Positive tourniquet test
– Petechiae, ecchymoses or purpura
– Bleeding
• Thrombocytopenia
• Evidence of plasma leakage
– Haematocrit >20% above average
– Decrease in haematocrit >20% after volume replacement
– Clinical signs (e.g. pleural effusion, ascites)
Dengue shock syndrome – All above are present, plus evidence of circulatory failure
• Rapid and weak pulse
• Narrow pulse pressure
– Hypotension
– Cold, clammy skin and restlessness

The major pathophysiological abnormality differentiating DF from DHF is the plasma leakage syndrome (haemoconcentration, hypoproteinemia and/or serous effusion). The severity of disease in DHF depends on the quantum of plasma leakage. Patients with DHF presenting with shock due to excessive plasma loss are labelled as dengue shock syndrome. DHF/DSS are potentially fatal conditions.

Clinical features – DHF/DSS is usually clinically indistinguishable from dengue fever during the initial phase of illness (Table 20). After 2-7 days, more serious manifestations of disease become apparent, reflecting disordered haemostasis and increased permeability. Capillary leak is caused by mediators like TNF alpha and IL-1 released from infected monocytes and macrophages. The capillary leak explains the rise in haematocrit, peripheral oedema, pleural effusion and ascites.

Capillary leak and thrombocytopenia may give a positive capillary test which is more than 20 petechiae in an area of 1 inch when the BP cuff is inflated midway between systolic and diastolic pressures for 5 minutes. Shock often occurs 24 hours before or after defervescence supporting a role for immune mediated injury. Encephalopathy, GBS and acute transverse myelitis have also been associated with dengue virus infection.

A coagulopathy may occur due to consumption of coagulant factors due to DIC, liver dysfunction and molecular mimicry between the viral proteins and coagulant factors.

Prognostic factors. BP 90/60, haematocrit 50%, platelet count < 50000, bleeding other than petechiae e.g. ecchymoses. haematemesis or epistaxis.

Grading of severity of dhf

I Positive tourniquet test and/or easy bruising

II Spontaneous bleeding

III Early signs of circulatory failure

IV Profound shock

Diagnosis – (a) Dengue antigen (NS1) detection test - NS1 Ag and Ab combicard - Rapid visual test for detection of dengue NS1Ag and IgM and IgG antibodies in human serum/plasma/whole blood. (b) Combination of both dengue antibody IgG and IgM with NS1 antigen is essential for diagnosis of early dengue fever and differentiate between primary and secondary dengue infection. NS1 is a glycoprotein produced by all Flaviviruses and is essential for viral replication. NS1 detection rate is higher in the acute phase of primary infection, it has been detected in serum of DENV as early as the first day post the onset of symptoms and remains positive upto 9 days.

Management – There is no specific antiviral therapy.

Treatment: For shock – Crystalloids like Dextrose normal saline or Ringer's lactate 10-20 ml/kg over 30 minutes, then every hr. till pulse, BP, CVP and urine output normalise. In profound shock initially colloids like hetastarch or haemaccel. Platelet transfusion for symptomatic thrombocytopenia.

Dengue fever – Paracetamol. Avoid aspirin because of increased bleeding tendency and risk of developing Reye's syndrome.

DHF/DSS – Plasma expansion with crystalloid solutions is the mainstay of therapy.

VIRAL HAEMORRHAGIC FEVERS

Viral haemorrhagic fevers – are acute illnesses characterised by fever and, in most severe cases, shock and bleeding.

Transmission – Person to person transmission to body fluids, and secretions or excreta.

Major viral haemorrhagic fevers

Lassa virus – The host is the rat Mastomys natalensis which excretes large amounts of virus in its urine.

Clinical features – Insidious onset with influenza-like symptoms. Abdominal pain, diarrhoea and vomiting may occur. Common physical signs are fever, pharyngitis and conjunctival injection. In severe cases bleeding begins towards end of first week. Hypotension and shock, encephalopathy and ARDS is seen in very severe cases.

Ebola virus – Initial symptoms resemble those of Lassa fever. A transient morbilliform, desquamative rash may occur. Hiccups are common.

Marburg virus – Clinical features resemble those of Ebola haemorrhagic fever.

Investigations – Specific diagnosis of these infections is by demonstrating the virus, antigen, IgM antibody, or a fourfold rise in IgG antibody in blood.

Treatment – Ribavirin reduces mortality if given in first week in Lassa fever Dose: 30 mg/kg iv loading dose, then 16 mg/kg iv 6-hrly for 4 days, then 8 mg/kg i.v. 8-hrly for 6 days (total duration of treatment 10 days).

Yellow fever, the prototype of viral haemorrhagic fever, is an acute infection characterised, by renal failure, cardiovascular collapse and bleeding. Causative agent, a mosquito-borne RNA virus belonging to the family Flaviviridae.

Transmission – A zoonosis transmitted between tree-hole-breeding mosquitoes and monkeys in forests of Africa and South America.

Clinical features – Spectrum of illness in yellow fever is variable, it ranges from nonspecific febrile disease which cannot be diagnosed without virological tests, to a severe infection characterised by liver and kidney failure, shock and haemorrhage.

Lab. findings – Neutropenia and thrombocytopenia, proteinuria elevated serum aminotransferases, and elevated bilirubin and creatinine, prolonged prothrombin time and partial thromboplastin time.

Investigation – Detection of virus in serum by ELISA or PCR. Virus can also be cultured from serum.

Management – is supportive.

10. CHIKUNGUNYA

Chikungunya fever is a viral disease transmitted by the bite of infected *Aedes aegypti* mosquito. The term is derived from Kungunyala meaning to become contorte or more specifically as 'that which bends up'. This refers to the stooped posture adopted by the patient as a result of arthritic symptoms. The disease is almost always self-limited and rarely fatal.

CLINICAL FEATURES

After incubation period of usually 3-12 days, there is sudden onset of flu-like symptoms including severe headache, chills, fever (>40°C, 104°F), arthralgia or arthritis, conjunctival suffusion, mild photophobia, nausea and vomiting. Joints of the extremities in particular become swollen and painful to touch. In some, joint pain is incapacitating and arthritis may last for weeks and months. Dermatological manifestations include a petechial or maculopapular rash on the limbs. Other features observed have been lichenoid eruption and hyperpigmentation in photodistributed areas, aphthous like ulcers over scrotum, crural areas and axilla, vesiculobullous lesions in infants, and subungual haemorrhage.

Acute chikungunya fever typically lasts a few days, but as with dengue and other arboviral fevers, some patients have fatigue lasting several weeks.

Diagnostic tests available are detection of antigen and antibody in blood by ELISA test. An IgM capture ELISA is necessary to distinguish the disease. Elevated levels of aspartate aminotransferases and C-reactive protein is seen.

Management. Treatment is symptomatic with relief of pain with ibuprofen, naproxen, aceclofenac or paracetamol. Aspirin should be avoided. Chloroquine phosphate 250mg/day has been found useful.

Chikungunya and pregnancy. There have been cases of mother-to-foetus infection between 2 and 4.5 months into pregnancy. IgG that is produced around day 15 passes through the placenta and confers immunity to the foetus. However, there is a possibility of risk of infection at birth if the virus is present in the mother's blood. Such infection in the foetus is rarely serious and majority recover quickly without sequelae.

11. HANTAVIRUS INFECTION

Aetiology. This bunya virus infects vascular endothelium and causes two major syndromes. The virus is acquired by exposure to aerosols of rodent urine and saliva and also faeces. Its manifestations can closely mimic either dengue or leptospirosis.

PATHOPHYSIOLOGY

Virus infection of the endothelium does not result in significant injury. Like dengue it is the immune response against viral antigens expressed on the endothelial cells in the heart, lungs, kidneys and lymphoid organs that causes most of the damage. This immune response is mediated by T cells and macrophages which release cytokines like TNF-alpha and IL-1 beta which increase capillary permeability and cause leakage of protein rich fluid into the interstitium. Nitric oxide released by TNF plays an important role in the vasodilation underlying the shock state. The virus however may damage renal tissues.

CLINICAL FEATURES

Cardiopulmonary syndrome (HCPS). Incubation period about 3 weeks. Illness begins with nonspecific constitutional symptoms that last about 3-7 days followed by a capillary leak syndrome that lasts for 3-7 days causing hypotension and shock. Leak into the pulmonary bed causes a noncardiogenic pulmonary oedema that can lead to rapid hypoxia, arrhythmias and cardiac arrest. There may be a separate oliguric phase lasting 3-8 days which precedes a polyuric phase lasting for a variable period of time.

DIAGNOSIS

Thrombocytopenia, leucocytosis, increased immunoblasts (upto 10% of circulating lymphocytes) with increased LDH is characteristic and should prompt diagnosis with more specific tests like ELISA for IgM and IgG antibodies.

Treatment is mainly supportive with IV fluids, inotropes, mechanical ventilation, extra-corporeal membrane oxygenation and blood products.

Haemorrhagic Fever with Renal Syndrome (HFRS)

The renal manifestations are more prominent than the pulmonary and renal injury occurs due to a combination of shock, immune injury and possible direct invasion by the virus. Nonspecific constitutional symptoms are followed by shock, oliguria, DIC and haemorrhagic manifestations. Survivors enter a diuretic phase by day 10-14.

Diagnosis involves similar parameters as HCPS.

Treatment includes both supportive treatment (including dialysis) and use of ribavirin.

12. JAPANESE B ENCEPHALITIS

This is an arbovirus encephalitis caused by a flavivirus that is transmitted to humans by bite of the *Culex mosquito*. Birds and pigs are the natural hosts of the virus and humans are dead end hosts.

PATHOPHYSIOLOGY

Most infections are asymptomatic with about 1 in 25 non-immune adults having symptoms. The virus can infect brain parenchyma (especially thalamus and basal ganglia) of the cerebral hemispheres, brain stem and anterior horn cells of spinal cord.

The spectrum of disease can present as mild flu-like illness, aseptic meningitis or severe encephalomyelitis. 50-60% of encephalitis survivors have neuropsychiatric sequelae with a high incidence in children compared to adults.

After inoculation into the skin the virus replicates in subcutaneous tissues, lymph nodes and blood stream before entering the brain. Previous infection due to other flaviviruses like dengue may protect against severe disease.

CLINICAL FEATURES

Patients with encephalitis present with altered sensorium, seizures and abnormal posturing. Severe brainstem injury can cause a locked-in state. Involvement of basal ganglia can present with a Parkinsonian syndrome, opisthotonus, choreoathetosis, myoclonic jerks and opsoclonus myoclonus.

INVESTIGATIONS

(a) Nerve conduction studies show reduced or absent compound muscle action potential with preserved sensory action potentials and normal conduction velocities. EMG is consistent with denervation. (b) Initial leucocytosis may be followed by leucopenia. (c) MRI is more sensitive than CT for showing characteristic lesions involving thalamus and basal ganglia.

Diagnosis is with an IgM capture ELISA or reverse transcriptase PCR of blood or CSF.

Prophylaxis – Japanese B encephalitis vaccine.

Treatment is nonspecific, only symptomatic for seizures and raised ICP.

Table 21: Differential characters of S. minus and S. moniliformis infection

	Spirillum minus infection	*Streptobacillus moniliformis infection*
Incubation period	5-30 days	2-10 days
Wound from bite	Recurrence of local lesion with each onset of fever	Local lesion at onset of disease, heals promptly
Lymph nodes	May be involved	Regional lymphangitis and lymphadenitis
Systemic manifestations	Regularly relapsing type of fever Generalised maculopapular rash in some cases Myalgia, no arthritis	Intermittent but not regularly relapsing fever Erythematous maculopapular rash in most cases Arthritis usually present
Laboratory tests	Isolation of spirillum by animal inoculation Agglutination test negative	Isolation by blood culture Agglutination with S. moniliformis positive

13. RAT-BITE FEVER

AETIOLOGY

Organism – Spirillum minus and Streptobacillus moniliformis. *Transmission* – Either of these infections in man may result from the bite of a rat but S. moniliformis infection may be acquired by swallowing material containing the organism, e.g. milk or infected food.

Incubation period – Average 2 weeks.

CLINICAL FEATURES

1. *Onset* – Sudden with often rigour, headache, high fever, pains in joints and muscles.
2. *Rat-bite wound* – Local response of allergic type with redness, swelling and oedema at site of bite with increase of discharge if not healed. Regional lymphangitis and lymphadenitis.
3. *Rash* – Dark purplish macular or maculopapular eruption over arms, legs, trunk and sometimes face. Rarely mucous membranes. May be absent. Rash fades during febrile periods and may reappear during relapses.
4. *Fever* – High remittent temperature for 4 to 5 days falling to normal with profuse sweats and subsidence of primary lesion. Recurrence of fever in few days but duration shorter. Such relapsing type of fever may continue for weeks or months in untreated cases. Usually paroxysms become less in height and duration and infection subsides spontaneously.
5. *Other symptoms* – Arthritis, delirium, rarely coma.

Differential characters of S. minus and S. moniliformis infection are given in Table 21.

DIAGNOSIS

S. minus – Leucocyte count normal or elevated. Organism may be visible on examination of blood or injection into peritoneum of mice or guinea pig; organisms will be visible 5-15 days later in blood or peritoneal fluid of the animal. S. *moniliformis* – Neutrophil leucocytosis. Organism may be isolated from blood or joint fluid. Agglutination tests positive in 2nd week.

TREATMENT

Benzathine penicillin 1.2 million units/day IM or Penicillin V 2 g/day orally for 7-10 days. If penicillin hypersensitivity, Erythromycin 2 g/day orally, or Tetracycline 2 g/day orally for 7 days.

14. LEPTOSPIROSIS

An acute infectious disease caused by *Leptospira interrogans,* highly motile, tightly coiled thin organisms with hooked ends. It is characterised by a broad spectrum of clinical manifestations, from unapparent symptoms to fulminating and fatal infection.

EPIDEMIOLOGY

(a) *Animal hosts* – Rats and small rodents are the most important reservoirs. Dogs, pigs, cattle, goats, wolves, foxes and other wild animals can also carry the organisms. (b) *Transmission* – Human infection results from contact with tissues of an infected animal or indirectly from contaminated water or soil. (c) *Routes of infection* – Moist or abraded skin, intact mucous membrane (nasopharynx, conjunctivae, vagina). (d) *Individuals at risk* – include sewer workers, abattoir workers, coal miners, farmers, fish workers and those employed on canals, docks and river drainage. Recreational water users (e.g. canoeists, windsurfers, swimmers, water-skiers) are also at risk. Infection via conjunctiva follows swimming or accidental immersion in contaminated water. In the home pet dogs can transfer the disease to children and adults through infected urine. Laboratory workers are at risk from handling animals.

PATHOPHYSIOLOGY

Most patients have a nonspecific febrile illness, but in a few the disease manifests with a severe illness characterised by hepatorenal dysfunction often with pulmonary haemorrhage (*Weil's syndrome*) which usually develops 4-9 days into the illness and is characterised by severe jaundice, bleeding (purpura or petechiae) and impaired kidney function and disorientation. The leptospires directly or through immune mechanisms damage blood vessels, cause centrilobular necrosis of liver, and renal tubular dysfunction by causing an interstitial nephritis and acute tubular necrosis. Renal function recovers completely by 6 months in most individuals.

Incubation period – 7-12 days.

CLINICAL FEATURES

Febrile illness *(first week)*

(a) **Septicemic phase** – Fever, headache, skin rash and myalgia simulate influenza and leptospirae appear in blood and CSF. Renal involvement is invariably present and ranges from urinary sediment changes and mild proteinuria to kidney failure in severe leptospirosis. Jaundice may be present. This stage lasts for 4 to 7 days followed within 48 hours by:

(b) **Immune phase** *(second week)* – lasts 4-30 days. Leptospirae disappear from all tissues except kidney and aqueous humuor in parallel with rise in circulating antibodies. Symptoms may include rash and secondary fever, meningeal symptoms, uveitis; hepatic and renal manifestations of febrile phase remain and may be more severe in some patients.

The following clinical spectrum can be seen in the second phase:

(i) *Haemorrhagic fever with renal syndrome.* Leptospirosis is an important infectious cause of ARF. Renal manifestations include an oliguric renal failure due to acute tubular necrosis or tubular interstitial damage leading to non-oliguric renal failure, high excretion of potassium and hypokalaemia, which can cause hyporeflexic paralysis. Widespread haemorrhages in GI tract, lungs, subarachnoid space and adrenals are also common because of extensive vasculitis.

(ii) *Atypical pneumonia syndrome.* Pulmonary symptoms and signs occur. Delayed resolution, small nodular densities and confluent areas of consolidation are radiological findings. Leptospirosis should be suspected in rapidly developing pneumonia with myalgia.

(iii) *Aseptic meningoencephalitis.* Sporadic cases of aseptic meningitis have leptospiral aetiology. Neurological manifestations include encephalitis and in rare cases hemiparesis.

(iv) *Myocarditis.* Cardiac dilatation, atrial fibrillation, cardiac failure and sudden death have been recorded.

INVESTIGATIONS

1. *Biochemical laboratory features* – (a) Leucocytosis with neutrophilia. (b) Thrombocytopenia. (c) Urinanalysis – Cellular elements, granular and pigmented casts and mild proteinuria. (d) Other tests done to confirm diagnosis are PCR, Indirect haemagglutination test assay (IHA) and IgM ELISA. IgM antibodies become positive by 5th day. MAT does not have any diagnostic significance in 1st week and peaks about 3rd week. (e) CSF may show aseptic meningitis like picture.
2. *Chest X-ray* – often shows dense confluent shadows suggestive of pulmonary haemorrhage.
3. *Serology* – Microscopic agglutination test (MAT) is the gold standard with either a fourfold rise in titres or a single titre of > 1:800 being diagnostic. Other serological tests are ELISA and a commercially available Dridot test which detects IgM antibody by an enzyme based dot immunoassay with a sensitivity of 30% at 3 days and of 100% at 10 days into the illness.
4. PCR assay – Positive in acute infection. Suggests antigenimia. Positive before antibodies appear in blood.

MANAGEMENT

Treatment should be started as soon as possible. (a) *Antibiotics* – Mild leptospirosis – Doxycycline 100 mg po bd, Amoxicillin 500 mg po bd Moderate/severe leptospirosis – Inj. Ceftriaxone 1g/day IM or by IV slow infusion for 7 days. Signs and symptoms may include rigours, high fever, low BP, headache and myalgias. (b) *Dialysis* – for kidney failure. (c) *Blood transfusions* and/or platelet transfusions may be necessary.

CHEMOPROPHYLAXIS – Doxycycline 200 mg once a week, Azithromycin 250 mg once or twice week.

15. ANTHRAX

Anthrax is a life-threatening zoonotic infection that normally affects individuals, especially ruminants. It is caused by *Bacillus anthracis.* The most common mode of infection is through the skin, which causes a painless sore that usually heals without treatment. If untreated cutaneous anthrax may progress in some cases to septicaemia with potentially fatal outcome.

Anthrax is a potential agent for use as a biological agent for terrorist activities however it is technologically difficult to use anthrax as a weapon on a large scale.

TRANSMISSION

Anthrax can be transmitted to humans by contact with infected animals or their products. It does not spread from person to person.

CLINICAL FEATURES

Anthrax can infect humans in three forms of the disease.

1. *Cutaneous anthrax* is the most common type and occurs when the spores or bacteria itself enter the body through a cut or abrasion. Symptoms begin to develop within 48 hours as a small, red, itchy papule at the site of infection. Within about 2 days it develops into a blister that eventually ruptures. The lesion ultimately dries into a coal-black scab (eschar). Some patients may have painful enlargement of lymphnodes, in some others infection can spread through the blood stream and prove fatal due to release of toxins.

   Diagnosis can be confirmed by Gram stained smears and culture of the material obtained from culture of the cutaneous lesion and blood culture.

   Tr. Ciprofloxacin or Doxycycline for 14 days.
2. *Inhalational anthrax* results from inhalation of spores into the lungs (wool sorter's disease). In the initial stages there is low grade fever, myalgia, malaise followed within 1-4 days by dyspnoea, haemoptysis, fever, cyanosis, pleural effusion, bronchopneumonia and coma.

   Tr. antitoxin monoclonal antibody raxibacumab is available with antibiotics.
3. *Gastrointestinal* anthrax can give rise to bloody diarrhoea which can be the cause of death.
4. *Fulminant meningitis.*

Prevention – Vaccination: anthrax vaccine adsorbed (AVA)

16. FILARIAL INFECTIONS

Filarial infections are caused by parasitic, tissue-dwelling, filarial nematode worms, which are transmitted by biting insects. Two main types of filariasis are:

1. Lymphatic filariasis transmitted by mosquitoes.
2. Subcutaneous filariasis (onchocerciasis and loiasis) transmitted by biting flies.

LIFE CYCLE – Adult female worms situated in various tissues in the human host produce embryonic microfilariae which are sucked up by mosquitoes or biting flies during a blood meal. Microfilariae develop to their larval stage in the insect vector and are passed on to a new human host in which the final maturation to adult worms takes place. Adult filarial worms do not multiply in man. See Figure 9 for the life cycle of W. bancrofti.

Periodicity of microfilariae – In most endemic areas the microfilariae of W. bancrofti appear in greatest numbers in peripheral blood in the night between 10 p.m. and 2 a.m., during the day they return to the pulmonary capillaries. Microfilariae of B. malayi exhibit either nocturnal periodicity or diurnal periodicity with a peak in the early evenings.

Lymphatic filariasis – can be caused by:

- *Wuchereria bancrofti,* transmitted by Anopheles, Culex and Aedes mosquitoes.
- *Brugia malayi,* transmitted by Mansonia and Anopheles mosquitoes.
- *Brugia timori,* transmitted by Anopheles barbirostris.

Clinical features – Two syndromes

(a) Lymphatic filariasis caused by adult or developing adult worms, producing episodic inflammation of lymphatic vessels, followed by obstructive lymphatic lesions.

(b) Syndrome caused by immune hyper-responsiveness of human host against microfilaria, producing occult filariasis (circulating filarial antigens or microfilaraemia).

ACUTE CLINICAL FEATURES

1. FILARIAL FEVER – Attacks of fever with rigours and with headache and malaise, lasting 3-7 days, recurring at intervals, and sometimes associated with an attack of filarial adenolymphangitis.
2. FILARIAL LYMPHANGITIS AND LYMPHADENITIS – (a) *Acute lymphangitis* – in extremities with fever with rigours and toxaemia. The tender inflamed lymphatics are seen as red streaks. It may be accompanied by itchy, irregular erythematous swelling of the skin scattered over the body, which may sometimes appear in absence of local lymphangitis. Lymphatics anywhere in the body may be involved, those of spermatic cord and testis are especially susceptible. (b) *Lymphadenitis* – occurs episodically, most often in inguinal area. Other sites are medial aspect of leg, axilla or medial side of arm. Occasionally in the breast. Involvement of intra-abdominal lymphatics may produce clinical appearances of acute abdomen.

   Secondary Gram-positive bacterial infections cause suppurative lymphadenitis or abscess formation particularly in the breast, or in muscle resembling tropical pyomyositis.

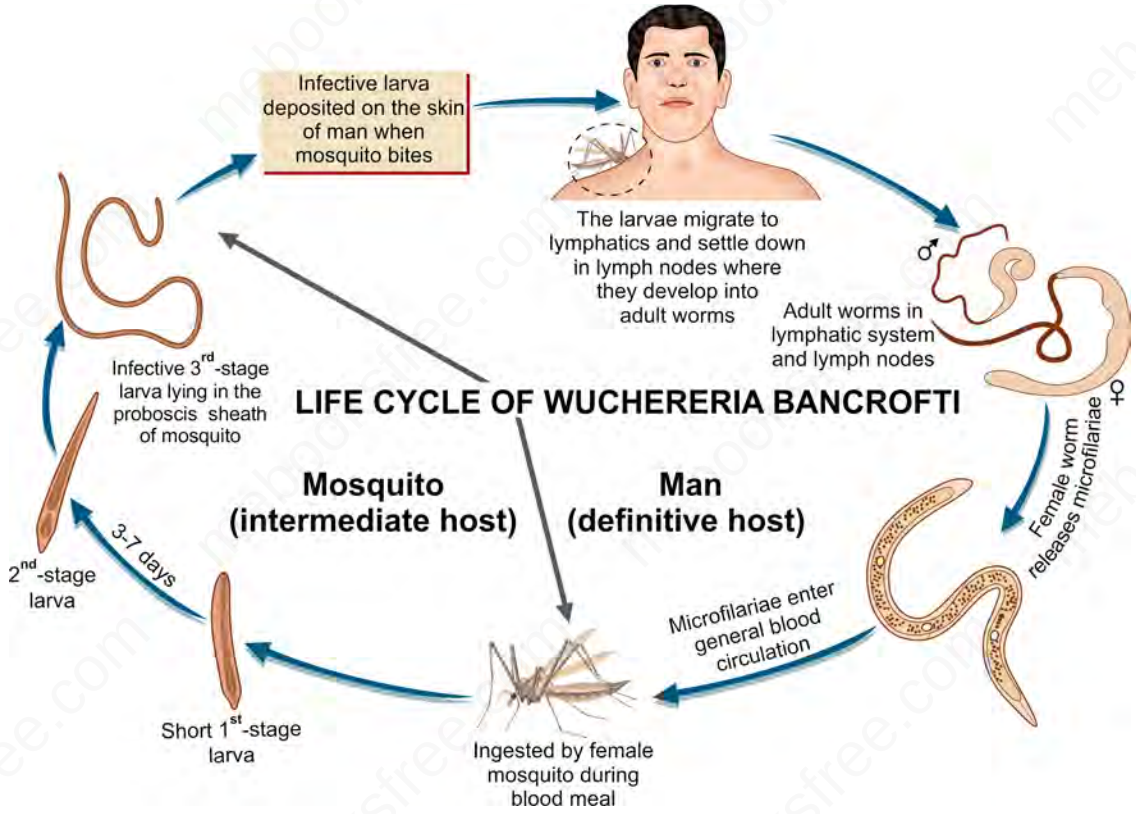


Fig. 9: Life cycle of Wuchereria bancrofti

Chronic Features (Late Obstructive Phase)

1. *Hydrocele* – is common with W. bancrofti.
2. *Lymphoedema* – is most common in lower limbs but also occurs in the upper limb or the breast.
3. *Elephantiasis* – results from further progression with dermatosclerotic and papillomatous changes superimposed. Lymphoedema and elephantiasis are much more pronounced on one side of the body, possibly because the parasites tend to congregate. Thickening of both skin and overlying tissues. One or both legs and scrotum most commonly involved. Upper extremities, breast and labia may also be affected.
4. *Rupture of lymphatic varices* – into renal pelvis or bladder gives rise to chyluria (when the lymph vessel is draining the intestine) or lymphuria (when it is not). Chyluria occurs intermittently and is more pronounced after a heavy meal. It is often symptomless, but may cause fatigue and weight loss due to loss of fat and protein.
5. *Tropical eosinophilic syndrome* – A hypersensitive reaction to lymphatic-dwelling parasites and characterised by chronic cough, wheezing and persistent eosinophilic count which may reach more than 50,000/µl. Increased specific serum IgE and characteristic histological lesions (Meyers-Kouwennar bodies) in lymph nodes, lungs, spleen and liver. Microfilaria are usually absent in blood. Chest radiography shows small-volume lungs with soft parenchymal infiltrates.

DIAGNOSIS

(a) Simple parasitological confirmation depends on finding the characteristic sheathed microfilariae in a thick blood film taken at the peak of periodicity of the strain (usually midnight) and stained with Mayer's haemalum (Fig. 10). (b) Enzyme-linked immunosorbent assay card test detects circulating W. bancrofti antigens, and W. malayi DNA can be detected using PCR analysis.

MANAGEMENT

1. Drugs – Diethylcarbamazine citrate (DEC) kills the microfilariae and a proportion of the adult worms of the lymphatic-dwelling filariae. A single dose of 6 mg/kg given annually is effective in the long-term killing of microfilariae and adult worms. It is usually given in mass campaign to reduce transmission, along with

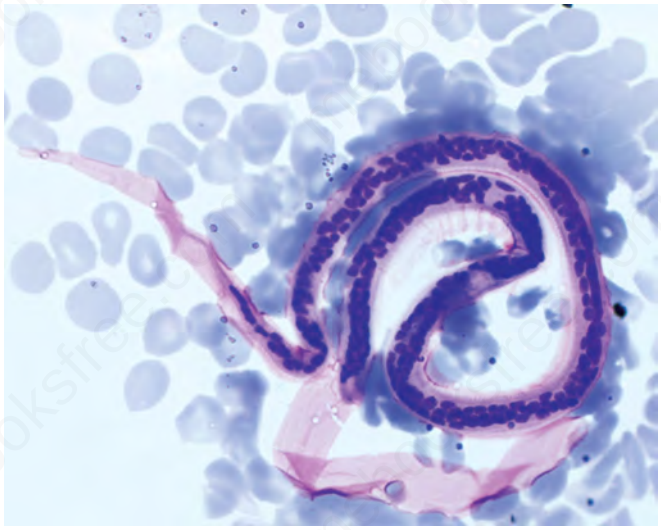


Fig. 10: Microfilaria in blood film

an annual dose of albendazole 400 mg which supplements its antifilarial action.

DEC must not be used in areas where onchocerciasis and/or loiasis are co-endemic. In these areas, the alternative is an annual dose of Ivermectin 150 mg/kg with albendazole 400 mg.

Use of DEC-fortified salt (0.2-0.4% w/w) for cooking and seasoning food over at least 9-12 months is a cheap, safe and effective means of eliminating lymphatic filariasis from an infected population.

Simple hygiene effective in preventing infection in secondary collateral lymph channels, which can re-establish lymph flow.

2. Palliative treatment
   (a) *Acute lymphangitis* – Rest, elevation of limb, hot fomentations, infra-red rays or short wave diathermy. Analgesics for relief of pain. Broad spectrum antibiotics to control infection.
   (b) *Chyluria* – Treated surgically.
   (c) *Elephantiasis* – Since bacterial and fungal infections trigger most episodes of adenolymphangitis in tissues with compromised lymphatic function, simple hygiene measures are – (i) Twice daily washing of affected parts with soap and water. (ii) Raising the limb at night. (iii) Working the foot up and down to promote lymph flow. (iv) Keeping the nails clean. (v) Wearing shoes. (vi) Use of antiseptic or antibiotic creams to treat small wounds or abrasions.

   Long-term low-dose DEC may also help to reverse chronic lymphoedema and elephantiasis. For resistant case lymphnodo-venous shunt operation, followed by surgical removal of excess tissue.

ONCHOCERCIASIS

It is a chronic filarial disease caused by Onchocerca volvulosus and transmitted by black flies of the genus Simulium. In mild infections there is pruritus with papulourticarial dermatitis. Generalised onchocerciasis presents with involvement of skin, eyes and lymphnodes. *Diagnosis* – confirmed by demonstration of microfilariae in skin snips, or cornea or anterior chamber (using slit lamp), or of adult worms in subcutaneous nodules. *Drug treatment* – Suramin kills adult worms, also DEC or ivermectin.

17. TROPICAL POLYMYOSITIS

This is a bacterial invasion of skeletal muscle usually due to *Staph. aureus.*

Pathogenesis involves the seeding of sites of muscle injury following transient bacteraemia. Large skeletal muscles such as the thigh, calf, gluteal and shoulder regions are typically involved.

Clinical stages. (a) First stage. Muscle pain, swelling and low grade fever. (b) Second stage 1-2 weeks later with progressive suppuration of muscle which may be followed by (c) Third stage of bacteraemia with complications like septic shock, endocarditis, pneumonia, pericarditis, septic arthritis, brain abscess and rhabdomyolysis.

Investigations. Leucocytosis. Blood cultures may be positive and serum CPK raised markedly.

Imaging with MRI or CT will often show abscess formation.

Tr. Cloxacillin 1-2 g iv or Cefazolin 2 g iv q8h. Addition of Clindamycin 600-900 mg iv q6-8h in mixed infection. Abscess drainage and debridement.

18. INTESTINAL HELMINTHS

Various worms that can infest humans are listed in Table 22.

HOOKWORM

Hookworms are nematodes belonging to the family Ancylostomatidae. Human infection is caused by *Ancylostoma duodenale* and *Necator americanus.* Transmission – may occur wherever faeces are allowed to remain in contact with damp soil at a suitable temperature.

Life Cycle

The first-stage larva hatches in 24-48 hours and develops in the soil to become the infective third-stage larva. It penetrates the skin and is carried in the blood to the heart and pulmonary blood vessels. It breaks out of the pulmonary blood vessels into the alveoli, then crawls up the trachea

Table 22: Worms infest humans

Infection Nematodes	*Parasite*
Filariasis	W. bancrofti (Bancroftian filariasis) Brugia malayi (Malayan filariasis) Loa loa (loiasis) Onchocerca volvulus (onchocerciasis)
Dracunculiasis	Dracunculus medinensis (guinea-worm)
Toxocariasis	T. canis or T. cati (visceral ocular larva migrans)
Trichinosis	Trichinella spiralis
Enterobiasis	Enterobius vermicularis
Hookworm infection	Ankylostoma duodenale (hookworm anaemia) Ankylostoma braziliensis or A. caninum (cutaneous larva migrans – creeping eruption) Necator americanus (hookworm anaemia)
Trichuriasis	Trichuris trichuria
Ascariasis	Ascaris lumbricoides
Strongyloidiasis	Strongyloides stercoralis
Trematodes (flukes)	
Schistosomiasis	Schistosoma mansoni Schistosoma japonicum Schistosoma haematobium
Fascioliasis	Fasciola hepatica (liver fluke)
Clonorchiasis	Clonorchis sinensis (oriental liver fluke)
Fasciolopsiasis	Fasciolopsis buski (intestinal fluke) Cestodes (Tape worms)
Taeniasis	Taenia saginata
Taeniasis/cysticercosis	Tinea solium (cysticercosis)
Diphyllobothriasis	Diphyllobothrium latum (fish tapeworm)
Hydatid disease cystic	Echinococcus granulosus
Hydatid disease alveolar	Echinococcus multilocularis

and enters the intestinal tract. Finally, it attaches itself to the mucous membrane of small intestine and matures into the adult worm.

Clinical Features

These are listed in Table 23.

Diagnosis

Detection of ova in faeces.

Treatment

When Hb is less than 5 gm% it is advisable to raise it to about 8 gm. with iron therapy before expelling the worms.

Table 23: Clinical features of hookworm infestation

Cause	*Clinical features*
Penetration of skin and subcutaneous migration of filariform larvae	Local erythema, macules, papules (ground itch)
Migration of larvae through lungs, bronchi and trachea to oesophagus	Bronchitis Pneumonitis
Injury to intestinal mucosal surface by attachment of adult worm	Anorexia Pica Epigastric pain and tenderness GI haemorrhage Diarrhoea (during acute invasion)
Sucking of worms causing chronic intestinal blood loss	Iron-deficiency anaemia Protein-losing enteropathy causing hypoalbuminemia and oedema
Chronic iron-deficiency anaemia	Exertional dyspnoea. Oedema
Loss of nutrients into intestine	Hypoalbuminemia, oedema Growth retardation
Iron deficiency	Impaired work productivity, learning, cognitive development.

Mebendazole – 100 mg bd for 3 days, not to be used in pregnant women or children < 2 years.

Albendazole – One dose of 400 mg for all patients over 2 years of age or

Pyrantel pamoate – 10 mg/kg (maximum 750 mg in adults) in a single dose for 3 days.

ROUNDWORM

(Ascaris lumbricoides)

Life Cycle

The eggs leave the body in the faeces. At this stage they consist of unsegmented ova protected by a thick shell, which in suitable conditions will develop into larval worms in 2 or 3 weeks. Man acquires the infection by swallowing the larvae, usually in contaminated food. The larvae hatch in the intestine, penetrate the wall, enter the blood stream and pass to the lungs. Here they leave the capillaries and enter the alveoli where they remain for about 10 days. They then pass up the air passages, down the oesophagus to the intestine where they grow to maturity.

Clinical Features

Tissue phase – Ingested larvae migrate from intestine to liver and lungs and provoke immunological and inflammatory reactions, e.g. – (a) Transient hepatomegaly. (b) Pneumonitis with symptoms varying from cough to severe dyspnoea and occasionally haemoptysis. (c) Loeffler's syndrome. (d) Bronchial asthma. (e) Urticaria.

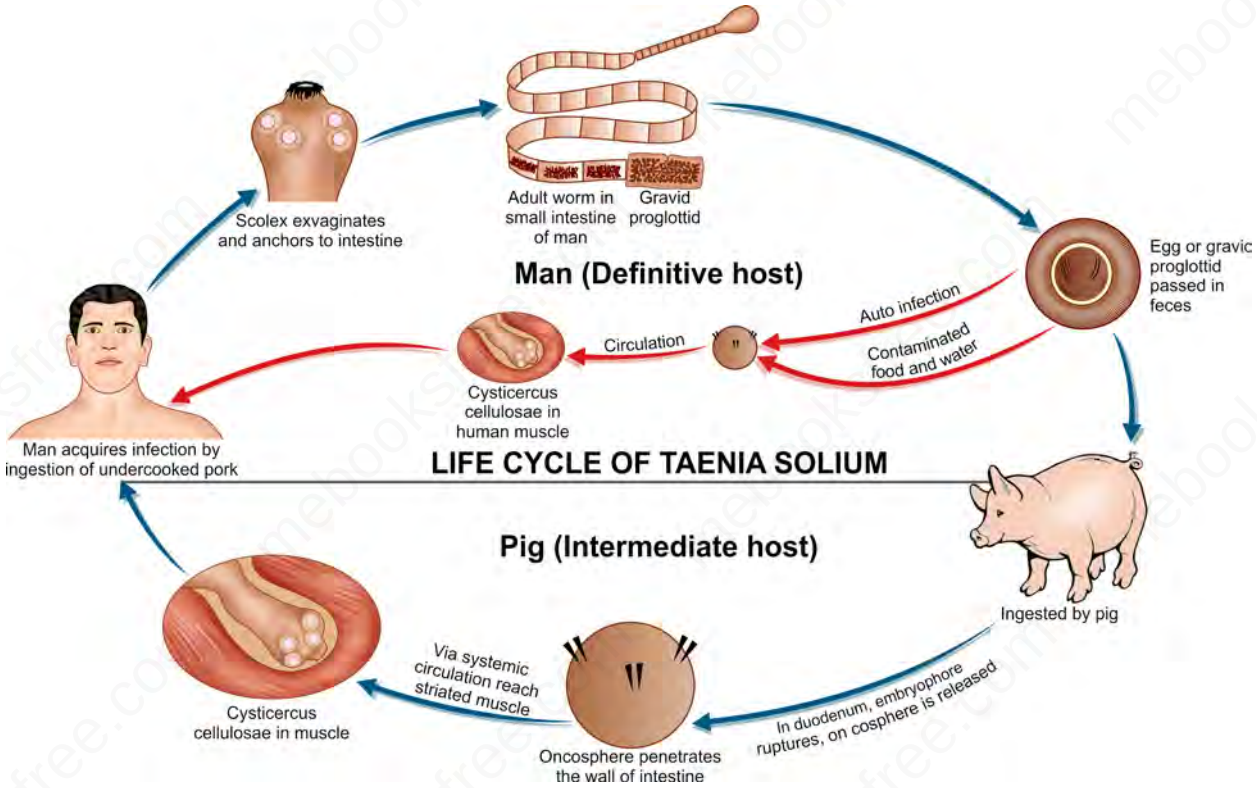


Fig. 11: Life cycle of Taenia solium

INTESTINAL PHASE – (a) *Intestinal ascariasis* – Intestinal colic and passage of worms in stools in mild to moderate infection. In heavy infections intestinal obstruction with at times perforation and volvulus may occur. In addition malabsorption, malnutrition and abdominal distension. (b) *Migration of worms* into orifices such as appendix, bile duct and pancreatic duct will produce signs of acute appendicitis, or clinical features of cholecystitis or pancreatitis. Worms that migrate from bile duct to hepatic duct and from there into the substance of the liver may die and form the focus of a hepatic abscess. Occasionally worms migrate to the stomach and are vomited, or migrate to unusual sites, such as the pharynx and are inhaled or block the Eustachian tubes.

DIAGNOSIS – (a) Finding adult parasites expelled from anus or mouth, or eggs in faeces. (b) Radiograph of gut – Adult A. lumbricoides may be seen. (c) In early ascariasis larvae may be found in sputum, there is marked eosinophilia and specific serological tests are positive.

TREATMENT

Mebendazole – 100 mg for 1 day only (for all age groups).
Albendazole – Children 2-12 years – One dose of 200 mg. Older children and adults – One dose of 400 mg.
Pyrantel pamoate – One dose of 10 mg/kg (maximum of 750 mg for adults).

TAENIASIS

(Tape worm) – is caused by either the beef tapeworm, Taenia saginata, or the pork tapeworm, Taenia solium.

T. saginata – is the commonest tapeworm affecting man. The larval stage (cysticercus) is found in beef and infection is acquired by eating beef containing a living cysticercus.

Life Cycle

When a living cysticercus is swallowed, the tapeworm head which it contains will emerge, attach itself to the mucous membrane of the upper jejunum and develop into a full-grown worm over the next 3 months (Fig. 11).

Symptoms

Segments of the worm are passed in stool or come out of the anus spontaneously. Other symptoms are weight loss, excessive hunger, abdominal pains and gurgling. Occasionally, straying proglottids may cause appendicitis or cholangitis.

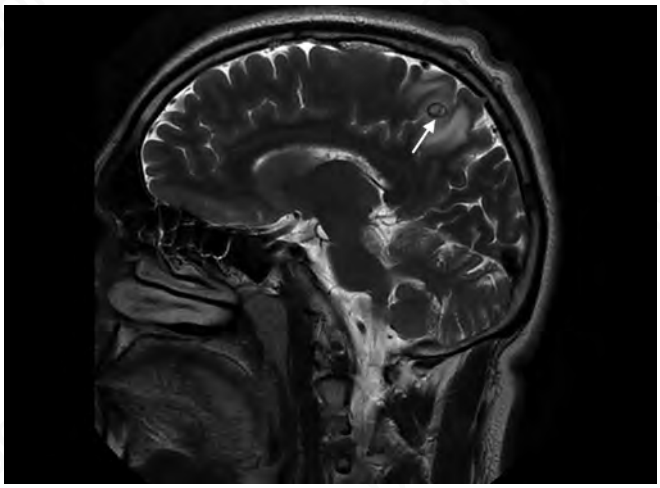


Fig. 12: MRI T2 image showing neurocysticercosis

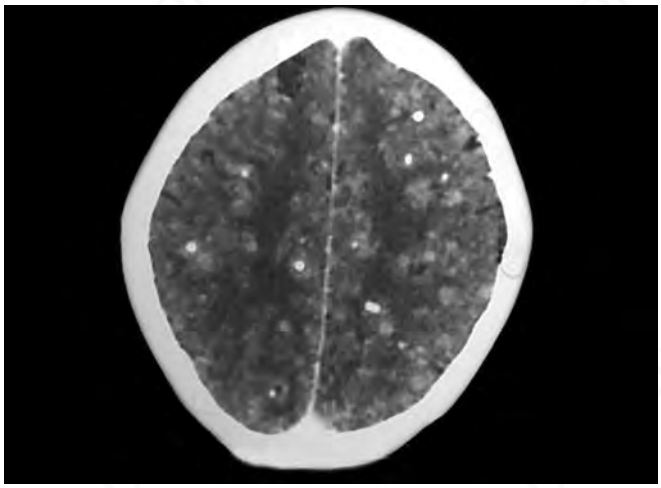


Fig. 13: Multiple neurocysticercosis showing 'starry sky appearance'

Diagnosis

Finding of proglottids or rarely scolex in stools. Eggs may be found in perianal area.

T. solium – Infection is caused by eating pork which contains a living cysticercus. Human cysticercosis arises either from swallowing T. solium eggs on contaminated food or by autoinfection from eggs produced by an adult worm in the host's intestine.

Life-Cycle

Life cycle resembles that of T. saginata except that hogs rather than cattle serve as intermediate hosts. Humans may also act as intermediate hosts.

Clinical Features

Infection with adult worm is usually asymptomatic. Heavy larval infection (cysticercosis) may cause:

1. ***Non-specific symptoms*** – during early stage of invasion by cysticerci such as fever, headache and urticaria with eosinophilia.
2. ***Localising symptoms and signs*** – (a) *Neurocysticercosis* – leads to intracranial hypertension and mental disorders, either separately or in combination (Figs. 12 and 13). Focal features such as ataxia, dysarthria are common and sudden death may occur. (b) *Skin and muscle* – Visible or palpable subcutaneous cysts felt as nodules of varying dimension especially in abdominal muscles and pectorals. (c) *Other sites* – (i) Eyes – Unilateral disturbance of vision. (ii) Liver and lungs may be involved.

Diagnosis

- Epilepsy (most common manifestation).
- Focal signs – Pyramidal tract signs, sensory abnormalities, signs of brain stem dysfunction. Increased intracranial pressure or dementia due to hydrocephalus or massive cysticercal infection of brain parenchyma. Muscular pseudohypertrophy due to massive infestation of skeletal muscles.

Diagnostic Criteria for Human Cysticercosis

Absolute criteria

- Histological demonstration of the parasite
- Direct visualisation of the parasite by fundoscopy
- Evidence of cystic lesions showing the scolex on CT or MRI ('hole-with-dot' image).

Major criteria

- Evidence of lesions suggestive of neurocysticercosis on neuro-imaging studies
- Positive immunological tests for detection of anti-cysticercal antibodies.
- Resolution of intracranial cystic lesions spontaneously or after therapy with albendazole or praziquantel alone.

Minor criteria

- Lesions compatible with neurocysticercosis detected by neuroimaging studies
- Demonstration of antibodies to cysticerci or cysticercal antigen in cerebrospinal fluid by ELISA
- Presence of clinical manifestations suggestive of neurocysticercosis
- Evidence of cysticercosis outside the central nervous system (cigar-shaped soft-tissue calcifications)

Epidemiologic criteria

- Residence in a cysticercosis-endemic area
- Frequent travel to a cysticercosis endemic a rea
- Household contact with an individual infected with Taenia solium

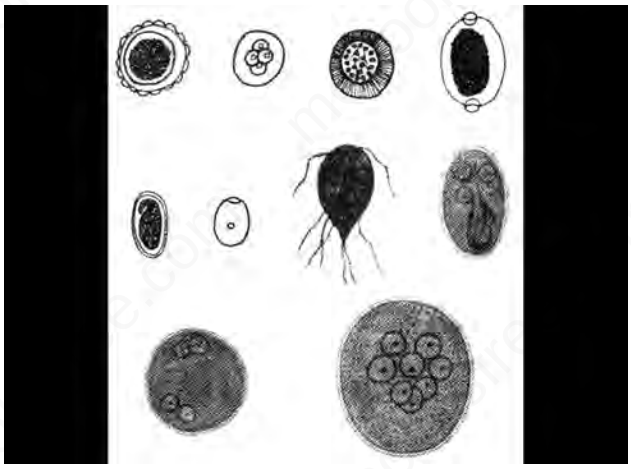


Fig. 14: Eggs of common in testinal worms

Diagnosis is confirmed by either one absolute criterion or a combination of two major criteria. one minor criterion and one epidemiologic criterion. A probable diagnosis is supported by the fulfillment of (1) One major criterion plus two minor criteria; (2) One major criterion plus one minor criterion and one epidemiologic criterion; or (3) three minor criteria plus one epidemiologic criterion (Fig. 14)

Management

Niclosamide – Adults – Single dose of 2.0 gm. Children under 5 years of age – Single dose of 0.5 gm. Older children – Single dose of 1.0 gm. The tablets should be given on empty stomach, chewed thoroughly and washed down with a little water. A purgative is recommended if the dead segments are not passed out within a few hours.

Mepacrine – for niclosamide resistant saginata. Dose 1 gm po or via nasogastric tube following by 5 mg metoclopramide iv.

Praziquantel – Single dose of 5-10 mg/kg after a light breakfast (all age groups).

For cerebral cysticercosis – Praziquantel 50 mg/kg/day for 15 days, or Albendazole 5 mg/kg/day for 30 days.

Corticosteroids are indicated in patients with cysticercotic encephalitis or angiitis, and in those with massive cysticercal infection of the brain parenchyma.

Treatment is considered successful when the scolex is found, no proglottids appear within 4 months of therapy in case of T. saginata, faecal examination remains negative for 3 months after treatment in case of T. solium.

ENTEROBIASIS

Is caused by the pinworm (thread worm) E. vermicularis. The adult threadworms live in the colon and rectum, and the gravid female emerges from the anus to deposit the eggs on the surrounding skin. These eggs if swallowed liberate the contained larvae which mature as they pass down the intestine.

Clinical Features

Minimal, except for anal and perianal itching. Heavy infestation may cause insomnia due to pruritus, anorexia and abdominal discomfort.

Complications

Appendicitis is a known intestinal complication. *Non-intestinal complications* – include vulvo-vaginitis in young girls and occasionally endometritis and chronic pelvic peritonitis due to granulomas formed round straying enterobius worms. Invasion of the urinary tract, which facilitates bacterial infection may cause enuresis. Some patients with protracted or recurrent infection have psychological problems.

Diagnosis

Adult female E. vermicularis, can be seen in perianal area, in faeces, or during proctoscopy or vaginoscopy. Presence of eggs can be demonstrated by applying adhesive cellophane tape to the perianal skin for microscopic inspection at night, removed and examined the next morning.

Treatment

Mebendazole – Single dose of 100 mg (all ages). Repeated after 2 weeks.

Pyrantel – Single dose of 10 mg/kg (maximum 500 mg). Repeated after 2 weeks.

Sporadic infections are usually cured by one treatment. In intensive and symptomatic infections, drug therapy should be repeated after 2 weeks, and then if necessary every 2 months.

Adjuvant measures – to prevent reinfection. Nails should be cut short and gloves and close-fitting sleeping drawers should be worn at night. Child's hands must be scrubbed with brush before meals. All infected members of the family should be treated simultaneously.

STRONGYLOIDIASIS

Is caused by the nematode *Strongyloides stercoralis.* Infection is acquired in the same way as hookworms and thereafter it is self-perpetuating.

Clinical Features

(a) *Asymptomatic.* (b) *Skin* – Penetration of larvae causes transient, linear, itching erythema. (c) *Respiratory* – Pneumonitis and Loeffler's syndrome (during lung migration).

(d) *Intestinal* – Ulcerative and/or haemorrhagic enteritis due to superficial inflammation of jejunal mucosa, resulting in severe hypoproteinemia and anaemia. (e) *Acute disseminated stronglyloidiasis* – may develop during pregnancy, puerperium, or in immunosuppressed subjects when it may prove fatal.

Diagnosis

Larvae of S. stercoralis may be found in sputum or in lung and jejunal biopsy samples, as also duodenal contents and faeces. ELISA for serum antibodies to antigens of Strongyloides is a sensitive method for diagnosing uncomplicated infections.

Treatment – Ivermectin is drug of choice. 200 mg/kg/day for 1-2 days or Thiabendazole 50 mg/kg/day in two doses for 2 days or Albendazole 400 mg daily for 3 days.

DIPHYLLOBOTHRIUM

Is acquired from consuming fresh water fish. Most infections are asymptomatic. Stool microscopy of eggs and inspection of stools for presence of proglottids are mainstay of diagnosis Tr. – Praziquantel 25 mg/kg as single dose or Niclosamide 2 g as single oral dose for adults.

TRICHURIASIS

(Whip worm) – It is a common infection of large intestine caused by *Trichuris trichuria*. The adult worms dwell in the large intestine with their thin anterior ends buried in the mucosa. Ova leave the intestine in the stools and after about 2 weeks are infective if ingested.

Clinical Features

(a) Mild infections are usually asymptomatic. (b) Less heavy infections may cause vague abdominal pain and diarrhoea. Iron deficiency anaemia may result from bleeding ulcers. (c) Severe massive infantile trichuriasis is characterised by protracted profuse mucus and bloody diarrhoea with abdominal pain, and rectal prolapse. Severe anaemia, digital clubbing, hypoproteinemia and growth retardation are not uncommon.

Diagnosis

Brown, barrel-shaped eggs with a plug at each end in the stools. In severe infection adult worms can be seen in rectal mucosa. Eosinophils and Charcot-Leyden crystals are often abundant in stools.

Treatment

Mebendazole – 100 mg/b.d. for 3 days or Albendazole single dose of 400 mg.

HYMENOLEPIASIS

Is caused by the dwarf tapeworm Hymenolepis nana and is a faecal-borne infection and can be long-lasting due to auto-infection. It is a common human tapeworm and is unique in having a direct human life-cycle, and autoinfection within the gut can occur.

Clinical Features

Common symptoms are weakness, weight loss, anorexia, abdominal pain and diarrhoea. Disturbances in protein digestion and absorption, protein-losing enteropathy, stunted growth and allergic phlyctenular keratoconjunctivitis may occur.

Diagnosis

Repeated examination of stools may be necessary to see the eggs.

Treatment

Niclosamide 60-80 mg/kg/day (maximum 2 g/day) for 5-7 days or *Praziquantel* single dose of 20 mg/kg for all age groups.

19. SCHISTOSOMIASIS (BILHARIZIASIS)

Schistosomiasis is a group of diseases affecting mainly the genitourinary and gastrointestinal systems and caused by trematodes of the genus *Schistosoma*. The three common species to infect man are S. haematobium, S. mansoni (predominantly human parasites) and S. japonicum.

Two more recently described species are S. mekongi and S. intercalatum.

PATHOGENESIS

When the cercariae penetrate human skin, they cause acute symptoms (swimmer's itch). This occurs a few hours to days after infection, and is probably related to the development of humuoral and cellular immunity to the cercariae. Few weeks later some patients experience a syndrome termed 'Katayama fever', which is thought to represent an immune complex disease, similar to serums sickness, as the immune response to schistosomal eggs begins.

The chronic features of schistosomiasis are organ-specific and related to the host response to deposited eggs. Egg deposition starts about 6-9 weeks after infection. Although the eggs are released into venous blood, many reach the lumen of the gut or bladder. Eggs reaching the lumen are excreted and subsequently hatch to form miracidia. Eggs not excreted lodge in the mucosa of bladder and bowel, and some reach the liver via the portal circulation. In the tissues, a cell-mediated response to the eggs leads to

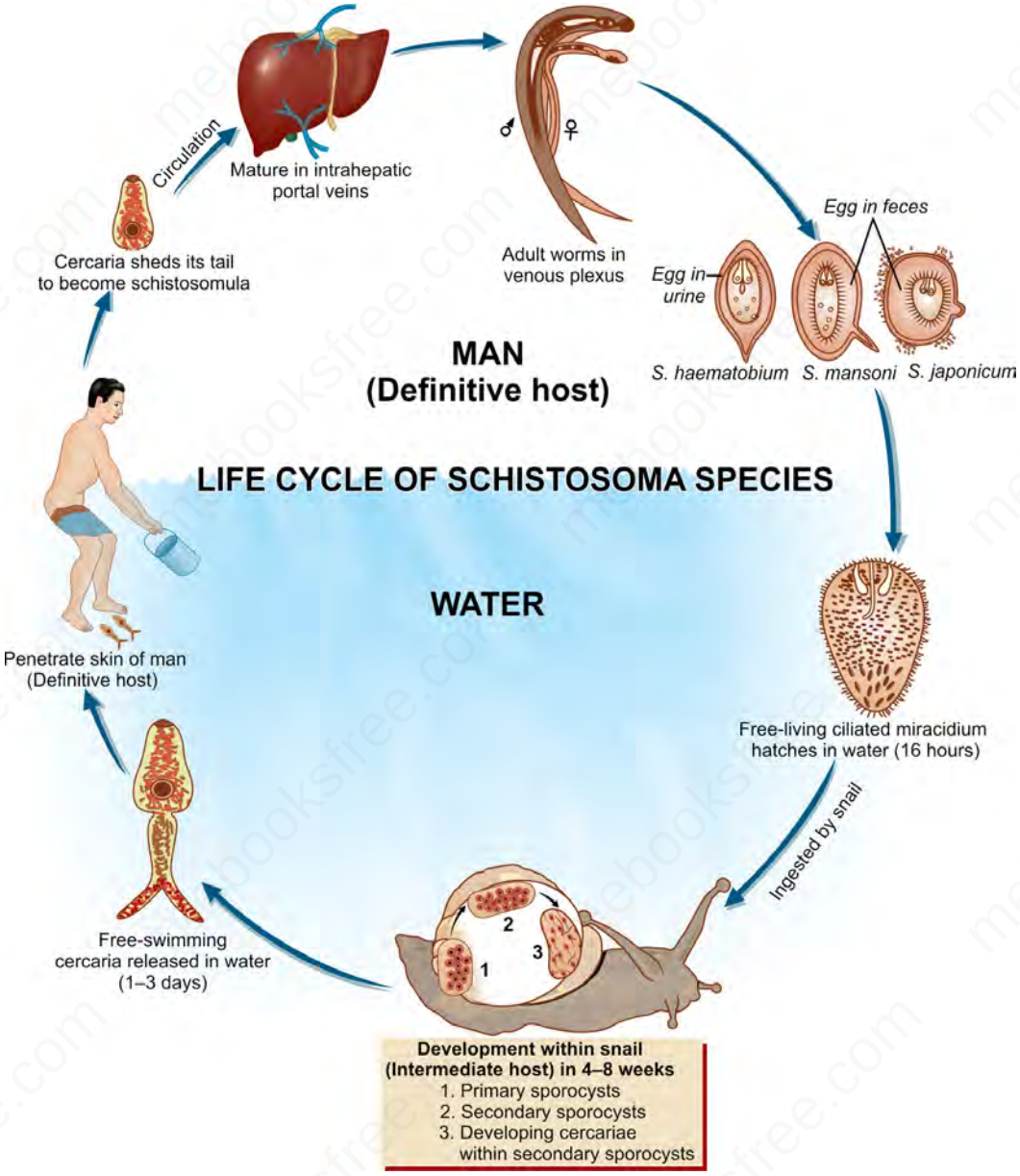


Fig. 15: Life cycle of Schistosoma spp

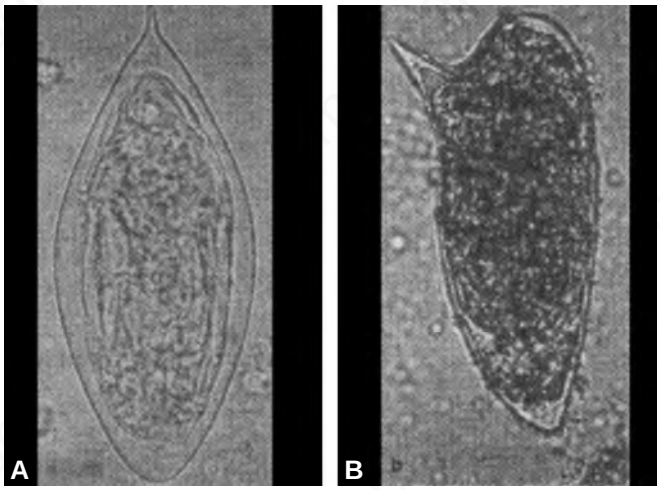
granuloma formation. See Figure 15 for the life cycle of Schistosoma.

CLINICAL FEATURES

Acute

Swimmer's itch occurs 1-2 days after exposure to fresh water containing cercariae. Affected individuals develop a macular, papular, itchy rash that lasts for few days before remitting spontaneously in those not previously exposed or a papular eruption in those with repeated exposures. It is mainly seen in association with S. haematobium.

Over subsequent weeks migration and maturation of the schistosoma can result in ***Katayama syndrome***. This typically presents with fever, headache, myalgia, abdominal pain and, occasionally radiographically opaque flitting pulmonary infiltrates occurring 14-84 days after exposure. This syndrome occurs more commonly with S. Japonicum. There is generalised lymphadenopathy and hepatosplenomegaly in this syndrome.



Figs. 16A and B: (A) S. haematobium infection is confirmed by finding the terminal-spined eggs in the urine. S. mansoni infection is confirmed by finding the lateral-spined eggs in the stoots

Chronic

Urinary tract – S. haematobium primarily causes dysuria, frequency and terminal haematuria. Renal ultrasonography may show bladder wall thickening, hydronephrosis and calcification in bladder and ureters. Cystoscopy may show 'sandy patches' on bladder mucosa.

Intestinal and liver disease – Infection with S. mansoni leads to egg deposition in intestinal mucosa and liver. Common symptoms are abdominal discomfort and/or diarrhoea. Egg deposition in liver ultimately leads to portal hypertension.

Other sites – (a) Lungs – Eggs may be deposited in the lungs, usually in patients with severe hepatic fibrosis. Multiple granuloma form in the lungs leading to cor pulmonale. (b) CNS – Eggs may migrate to the brain causing generalized or focal seizures. (c) Renal – Chronic glomerulonephritis. (d) Skin – Nodular rash from eggs migrating to skin.

DIAGNOSIS

(a) Eggs of S. haematobium are often seen in urine. Eggs of other schistosomal species may be detected in faeces. Biopsy of affected tissues (e.g. rectal biopsy) can also demonstrate eggs. (b) Serological tests are sensitive but are not useful for detecting active infection (Figs. 16A and B).

MANAGEMENT

Praziquantel 40 mg/kg in a single dose. The drug is well tolerated. Main side-effects are abdominal pain, and sometimes nausea and vomiting. In patients with CNS involvement, simultaneous use of corticosteroids.

20. HYDATID DISEASE

Hydatid disease of man is zoonosis caused by infection with tapeworm larvae of the genus *Echinococcus*.

There are two forms – (a) Cystic: The much more common *E. granulosus* causes unilocular hydatid cysts and is widespread in dogs and livestock (sheep, goats, cattle and camels) and in man. (b) Alveolar: caused by *E. multilocularis*, the 'malignant' hydatid is transmitted between foxes and rodents, but is very rare in humans.

LIFE CYCLE OF ECHINOCOCCUS

The adult worm lives in the small intestine of the dog. Eggs are shed in the faeces and ingested by sheep, usually from contaminated pasture. The eggs hatch in the duodenum and larvae migrate through the gut wall. Blood stream dissemination follows usually to the liver.

CLINICAL FEATURES

Hydatid cysts especially if calcified may be asymptomatic and first noted incidentally during routine physical examination. Symptoms and signs depend on the organ affected.

1. **Liver** – Hydatid cyst may present as:
   - Painless hepatomegaly.
   - Pyrexia of unknown origin following secondary pyogenic infection.
   - Jaundice due to pressure on the bile ducts.
   - Severe systemic reaction following rupture into peritoneal cavity, gut itself or pleural cavity.
   - Cholangitis from rupture into biliary tree.
2. **Pulmonary**

   Primary
   - Solitary or at times multiple cysts on plain radiograph.
   - Shortness of breath or chest pain if cyst is large.
   - Haemoptysis following ulceration into a bronchus.
   - Expectoration of watery fluid and daughter cysts ('grape skin' expectoration) following rupture into the bronchial tree.
   - Respiratory distress due to aspiration of fluid elsewhere in the lungs, may be associated with urticaria and anaphylactic shock.
   - Fever, cough and purulent sputum, if secondary pyogenic infection occurs.

   Secondary (metastatic) – A rare form due to breaking of a primary visceral cyst into a vein or heart.

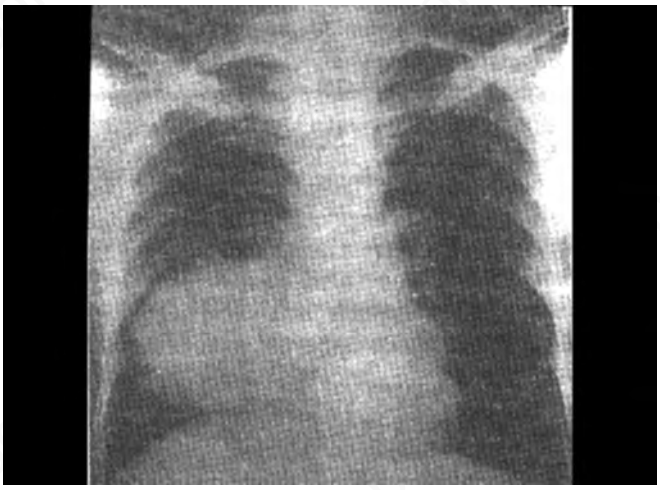


Fig. 17: Hydatid cyst of lung. Homogeneous rounded opacity

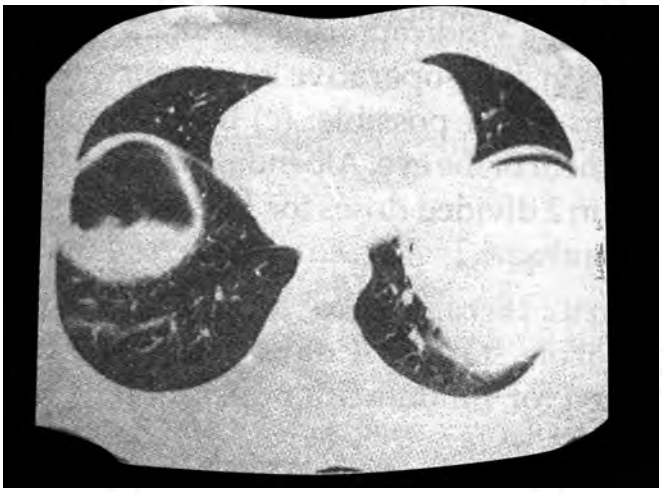


Fig. 18: HRCT thorax showing one hydatid cyst in right lung with water lily sign and another cyst in left lung

3. **Cerebral**
   - Seizures or signs of increased intracranial pressure of subacute onset and progressive course that resembles slow-growing brain tumour. Neurological manifestations tend to evolve more rapidly with alveolar hydatid disease.
4. **Spinal cord**
   - Root pain and motor or sensory deficits, may be seen in both cystic and alveolar disease.
5. **Orbital**
   - Unilateral proptosis.
6. **Abdomen**
   - Pseudocyesis from rapidly growing cysts.

INVESTIGATIONS

1. Imaging

   Chest radiograph – (a) Classical appearance of a circular shadow sharply defined with no reaction in surrounding lung parenchyma (Fig. 17). The cyst may change shape on maximum inspiration and expiration (Escudero nimerove sign). (b) Crescent sign or pulmonary meniscus sign – If the cyst communicates with a bronchus, a cap of air may be seen above the cyst (also seen in lung abscess partially filled with inspissated pus or blood clot, tuberculous cavity containing a Rasmussen aneurysm, and in intracavitary fungal ball). (c) Double arch (Cumbo's) sign – As more air enters between pericyst and endocyst, the shrinking cyst ruptures with resultant air fluid level within the endocyst capped with crescent of air between pericyst and endocyst. (d) Water lily sign – With further separation of endocyst and evacuation of fluid, a wavy endocyst membrane floats on top of remaining fluid. (e) Membrane sign – Introduction of contrast medium which enters the layers of the ruptured hydatid membrane produces a radiolucent undulating line (lucent membrane sign).
2. HRCT thorax (Fig. 18).
3. Ultrasonography – for detection of hepatic cysts. Cystic hydatid disease is usually characterised by large, unilocular, liquid-filled vesicle that is well demarcated from surrounding brain or liver parenchyma. Hepatic hydatid cysts can be classified into: (a) Univesicular hypodense cyst containing 'hydatid sand'. (b) Univesicular hypodense cysts with double or undulating membrane. (c) 'Mother and daughter' cyst which is highly specific for hydatidosis. (d) Detachment of the germinal layer which produces classical 'Water lily' sign. (e) Cyst wall calcification. (f) CT scan is useful to visualize the relation of the hydatid cyst to surrounding liver tissue, bile ducts, portal and hepatic veins and its segmental location (Fig. 19).

   Immunological diagnosis – by ELISA can be helpful but is not always accurate, because of cross-reactions with other parasite infections. ELISA has about 90% sensitivity for hepatic cysts of E. granulosus. Detection of circulating antigens by immunoblot may be of diagnostic value in some cases particularly in those with false-negative ELISA.

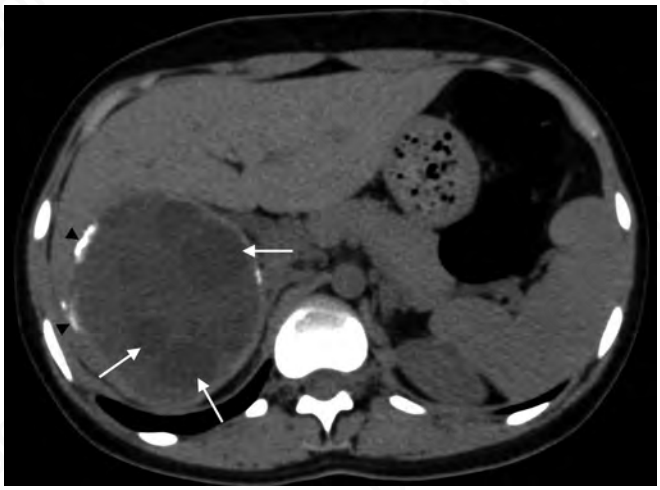


Fig. 19: Hydatid liver disease with daughter cysts (white arrow) and calcific wall (black arrow head)

SEROLOGY

Unlike ADA, white cell count is usually normal unless cysts are leaking or infected. LFTs commonly show an obstructive picture. Eosinophilia if present, suggests the cyst has recently ruptured or leaked.

MANAGEMENT

1. *Operative surgery* – for removal of cyst. Leakage of hydatid fluid should be avoided to prevent anaphylactic reaction. The type of operation can be pericystectomy, lobectomy or pneumonectomy is decided at time of operation.

   If surgery is not an option, single cysts that are easily accessible, an alternative approach is percutaneous drainage with installation of sclerotic substance (usually ethanol), a technique known as PAIR (percutaneous aspiration, injection and re-aspiration). Medical treatment alone has low cure rates and most patients require additional surgery or PAIR. 15 mg/kg body wt/day in two divided doses for 3 weeks every month for 6 months.
2. *Chemotherapy* – Indications – (a) Inoperable hydatid disease. (b) Post-operative recurrence when re-operation is not possible. (c) Multiple cysts. (d) Involvement of the eye. Albendazole 15 mg/kg body wt/day in 2 divided doses for 3 weeks every month for 6 months.
3. *Combined therapy* – Along with surgery Albendazole starting 4 days preoperatively and continued for 1 month after operation.

21. DRACUNCULIASIS (Guinea-Worm disease)

Human dracunculiasis is caused by infection with meter-long round worm D. medinensis.

LIFE CYCLE AND PATHOGENESIS

The adult female D. medinensis lives in subcutaneous tissue. About a year after infection, transient fever and dermatitis occur, and the gravid female worm can be seen migrating just under the dermis. A chemical irritant released from the worm's uterus results in formation of a blister above the anterior end of a worm, filled with motile first-stage larvae; this is usually accompanied by symptoms of anaphylaxis. When sufferers enter ponds or wells to 'cool' the affected limb or fetch drinking water, the blister ruptures and releases thousands of larvae which are ingested by several species of crustaceans in which they become infective after about 2 weeks. Following ingestion by human host, larvae undergo several molts. Mating and maturation occurs in deeper tissues and body cavities, and then maturing female worms return to the subdermis to complete the 12-15 month prepatent period.

CLINICAL FEATURES

Prodromal symptoms – Transient fever and dermatitis before appearance of mature worm migrating in subcutaneous tissue, or subcutaneous blister which appears as a reddish papule on the extremities or trunk.

Secondary infection – Exit lesions become secondarily infected. Attempts to extract the complete worm often causes it to rupture; large amounts of protein are thus released into the wound site, exacerbating inflammatory processes and resulting in painful abscesses. Chronic recurrent infection may cause ankylosis of joints. Gangrene and tetanus may develop.

Cryptic infection – Symptomatic infections with adult worms in sterile deep tissue, abscesses in ectopic sites frequently occur with or without the presence of emerging worms. Most commonly, these worms are subdermal, or are located in axial lymph nodes, scrotum, or in intramuscular sites. Neurological manifestations include subdural abscesses with paraesthesiae, and paralysis.

INVESTIGATIONS

(a) Motile first-stage *larvae* – may be recovered from superficial abscess exudates and seen microscopically on wet mount. (b) *Adult worm* – Remnants of adult worm cuticle surrounded by granulomatous tissue or calcification

may be seen in surgical specimens from deep tissues. (c) *Serological tests* – ELISA can detect antibodies in patients with cryptic or prepatent infections.

MANAGEMENT

Minor surgical enlargement and firm massage along the tract of the worm can facilitate removal of emerging worms. The worm is wound on a rod, few centimetres each day, avoiding excessive tension. Septic abscesses and anaphylaxis require appropriate therapy.

TISSUE NEMATODES

Toxocariasis results from dog roundworm *Toxocara canis* or cat roundworm *T cati*. Infection manifests as

1. Visceral larva migrans more common in children, in whom pica is a risk factor. Cl. Fs.: Anorexia, abdominal pain, fever, hepatomegaly, cough and wheeze. Tr. Symptomatic and anthelminthic (albendazole, diethylcarbamazine).
2. Ocular larva migrans. Cl. Fs.: Asymptomatic or visual loss, squint, fixed pupil or a red eye. On examination, posterior chorioretinitis with a mass lesion, or peripheral intraretinal granuloma.

Trichinosis is caused by infection with *Trichinella spiralis,* for which humans are 'dead-end' hosts. Cl. Fs.: Most infections in humans are asymptomatic, or with symptoms in 2 phases:

(a) Intestinal phase with nausea, vomiting, abdominal cramps and diarrhoea, occasionally bloody.

(b) Extraintestinal phase with prominent muscle invasion. Common symptoms are fever, myalgia, periorbital oedema and headache, and occasionally macular or petechial rash. Myocarditis is potentially fatal, and CNS involvement may lead to fits, paralysis, coma and death. Tr. Albendazole or thiabendazole.

Angiostrongylus infection. Human infection occurs from ingestion of salads contaminated with larvae contained in mucus from snails or undercooked dishes containing snails, crabs or prawns. Cl. Fs.: Meningitis, papilloedema, extraocular n. palsies and cerebral abscess. Tr. Albendazole.

Gnathostomiasis. Gnathostoma spinigerum is a parasite of feline and canine hosts. Humans become infected after eating undercooked fresh water fish, frogs or snakes. Cl. Fs.: Larvae can cause intermittent subcutaneous swellings, pleural effusion, abdominal pain, eosinophilic meningitis or myeloencephalitis. Tr. Albendazole.

22. TROPICAL SPRUE

It is GI dysfunction characterised by deficiency in gastric secretion and inability to absorb adequately fat, glucose, calcium and certain other food constituents and characterised by morning diarrhoea, bulky gaseous stools, sore tongue, megalocytic anaemia and wasting.

AETIOLOGY

Age – usually middle age. *Sex* – more in females especially when pregnant. *Geographical distribution* – Tropics and subtropics and mainly in hot, damp coastal climates. *Season* – Onset usually after rains. *Race* – mostly amongst Europeans. *Other predisposing causes* – Prolonged residence in endemic area and hills, chronic dysentery, mucous colitis or hill diarrhoea. *Cause* – An alimentary dysfunction in which a series of interlocking pathophysiologic events occur.

CLINICAL FEATURES AND DIAGNOSIS

See Malabsorption syndromes.

Course – Sprue relapses are uncommon after adequate treatment (unlike idiopathic steatorrhoea) and when they do occur, ultimately respond to treatment. Fatal cases are rare.

DIFFERENTIAL DIAGNOSIS

1. *Other megaloblastic anaemias.*
2. *Idiopathic steatorrhoea* –Long history. In sprue onset and course often more rapid, diarrhoea almost invariable, anaemia tends to be more severe and is commonly normochromic or hypochromic. Hypocalcemia and cramps uncommon, stomatitis more marked, anorexia and abdominal pain more common. No specific response to folic acid or antibiotics.
3. *Chronic pancreatitis* – Faeces contain high percentage of neutral fat but split fat content low, the reverse is true in sprue.
4. *Giardiasis* – may cause steatorrhoea. Diagnosis made by finding cysts of the parasite in formed stools and vegetative forms in fluid stools.
5. *Intestinal strictures* – e.g. due to TB.

MANAGEMENT

Aims – (i) Rest to alimentary canal by dietary regime. (ii) Correction of anaemia and gross deficiency conditions.

1. *Diet* – High protein, low carbohydrate and low fat – (a) Milk diet – Skimmed milk or Proprietary dried milk; or protein hydrolysates and concentrates; 2 hourly feeds. Fruits and glucose. (b) Mixed diet – Skimmed milk, eggs, meat, bread, green vegetables, fresh fruits, and milk pudding.
2. *Folic acid* – Effect most marked in cases with prominent megaloblastic anaemia. 30 mg day po or 15 mg IM for 3 weeks controls diarrhoea and causes improvement in stomatitis and glossitis. Maintenance dose of 5 mg bd. The effect on fat absorption defect is minimal.
3. *Antibiotics* – Short course treatment with broad spectrum antibiotics such as oxytetracycline 250 mg qds by mouth can be effective.
4. *Corticosteroids* – if folic acid therapy fails. Prednisolone 50 mg/day for 7 days, dose gradually reduced to 15 mg/day.
5. *Treatment of anaemia and other deficiencies* – (a) Vitamin B_{12} 50-100 mcg twice a week together with folic acid for optimal haemopoietic response. (b) Vitamin B complex. (c) Pancreatic enzyme tablets 0.4 gm bd after meals. (d) Calcium salts and vitamin D. (e) Transfusions in severely anaemic patients.

23. EFFECTS OF HEAT

High environmental temperature with high relative humidity can result in heat syndromes.

CLINICAL MANIFESTATIONS

1. **Heat fever** – is common in the aged and in children in summer months. Fever is continuous in the range of 101°-104°F and may have a spontaneous onset or follow about a week after surgery. A change in the mental state of the patient (apathy, drowsiness) may occur after about a fortnight of pyrexia with tremulousness of the hands and increased tone in the extremities. Drowsiness may progress to coma and if undiagnosed may result in death.

   Tr. – Shifting the patient to cooler environment and maintenance of electrolyte balance.
2. **Heat cramps** – of striated muscle from excessive salt loss due to profuse sweating in high environmental temperatures. It is common in boiler room workers, steel workers and miners. Calf muscles are most commonly affected but cramps may occur in the chest, and when affecting abdominal muscles simulate an acute abdomen.

   Tr. – Cramps can be rapidly relieved by drinking fluids containing sodium chloride or by 1/2-1 litre of normal saline IV.
3. **Heat syncope** – A fainting spell or 'blackout' from excessive heat and humidity. The individual drops to the ground if standing and there is transient loss of consciousness.

   Tr. – Lying down flat in cool surroundings is followed by quick recovery.
4. **Heat stroke** (Sunstroke, heat hyperpyrexia) – Characterised by sudden loss of consciousness which may be preceded by prodromal signs typical of cerebral irritation – headache, dizziness, nausea, convulsions, and visual disturbances. Failure of the heat regulating centre gives rise to high fever and cessation of sweating. On examination the skin is hot and flushed and dry, pulse rapid, irregular and weak and low BP. Temperature may reach as high as between 105°-107°F. If the patient is not treated the temperature continues to rise and a state of hyperpyrexia supervenes. Rhabdomyolysis, cardiac dysrhythmias, acute renal failure and coagulopathy ensue and contribute to the high mortality rate.

   Management – (a) Cooling by fanning after sprinkling with water. Immersion in cold water or use of ice packs or ice water enemas. (b) Massage of extremities to maintain circulation. (c) Sedatives contraindicated unless convulsions. (d) Normal saline 1000 ml IV slowly if dehydration or cramps.
5. **Heat exhaustion** – Three types:

   (a) ***Due to anhidrosis*** – Due to acute heat stress after long residence in tropics; may follow prickly heat. Feeling of heat and exhaustion and headache, giddiness and palpitation. Fever 99°-100°F, tachycardia and increased respiratory rate. Collapse and coma may occur.

   Management – Removal to cool surroundings.

   (b) ***Due to salt deficiency*** – Predominant salt depletion prone to occur during periods of acclimatisation. Anorexia, nausea, vomiting, syncope, giddiness, painful spasms of muscles of abdomen and extremities. Skin moist and cool, pulse rapid, and low blood pressure. Circulatory failure or sudden collapse may follow.

   Management – Half-strength normal saline by mouth with fruit juice, normal saline IV.

Table 24: Differentiation between heat stroke and heat exhaustion

	Heat stroke	*Heat exhaustion*
Cause	Inadequate or failure of heat loss	Depletion of fluids and electrolytes
Warnings	Headache, weakness, sudden loss of consciousness	Gradual weakness, headache, anorexia, faintness
Clinical features	Hot, red, dry skin. Little sweating, tachycardia, hyperpyrexia	Pale, cold, clammy skin, weak pulse, hypotension

(c) ***Due to water deficiency*** – Syndrome of predominant dehydration with elevated serum sodium. Usually seen during illnesses which prevent proper intake or absorption of water e.g. cardiac or cerebral disease. Intense thirst main complaint. Also lethargy, fatigue, irritability, abdominal discomfort and tingling in the limbs with ultimately mental confusion and muscular incoordination.

Management – Large amounts of water by mouth, or IV 5 per cent glucose. Since the total body sodium is likely to be reduced, sodium depletion may occur during phase of rehydration and salt-containing drinks should be administered as soon as improvement is observed.

Table 24 shows differentiating features between heat stroke and heat exhaustion.

6. **Heat oedema.** Swelling of ankle and wrist can occur in first 4 days of heat exposure which disappears after acclimatisation.
7. **Exertional heat disorders.** Physical exertion (e.g. marathon runners) in hot and humid condition can cause headache, fever, diaphoresis, nausea and vomiting and muscular incoordination and hypotension and tachycardia. *Tr*. control of fever with cold water sponging, massage of the extremities and IV infusion of 5% dextrose in saline.

24. ENDEMIC FLUOROSIS

A disease entity resulting from ingestion of excessive quantities of fluoride in drinking water over a prolonged period. It primarily affects hard tissues of the body manifesting as mottling of enamel and osteosclerosis of the skeleton.

FACTORS INFLUENCING TOXICITY OF FLUORIDE

1. *Fluoride concentration of drinking water* – is the most important factor.
2. *Duration of exposure.*
3. *Occupation and sex* – Most cases of skeletal fluorosis occur in those doing hard manual labour. Incidence is higher in males.
4. *Nutrition* – Poor nutrition particularly lack of proteins and calories.
5. *Climate* – Hot climate favours increased ingestion of water which may contain excess fluorine.

CLINICAL FEATURES

1. ***Dental fluorosis*** – 'Mottled enamel' due to dental hypoplasia with areas of hypocalcification best seen on incisors of upper jaw. Besides brownish discolouration there is pitting of enamel surface.
2. ***Skeletal fluorosis*** – (a) *Symptoms* – Pain and rigidity of spine and later on of joints. Paraesthesiae in limbs. (b) *Skeletal changes* – (i) Irregular bone deposition may be felt as exostosis along anterior borders of tibia, near tibial tubercle, olecranon and along medial border of scapula and near the vertebral spinous processes. (ii) Fixed flexion deformity from ossification of interosseous membrane of forearm and leg. (iii) Kyphosis.
3. ***Neurological complications*** – (a) Due to compression of spinal cord – Paraesthesiae with patchy sensory involvement, weakness, wasting and fasciculations with spasticity and loss of sphincter control. (b) Uncommon features – Cerebrovascular insufficiency or cerebellar ataxia from compression of vertebral artery in spine, peripheral neuritis, headache, nerve deafness.
4. ***Urinary system*** – (a) *Acute poisoning* with fluorine causes polyuria, excessive thirst, nocturia and frequency of micturition (Diabetes insipidus fluorique). (b) *Chronic ingestion* – may lead to chronic nephritis, and kidney failure.
5. ***Soft tissue lesions*** – (a) Thyroid goitre due to iodine deficiency since fluorine competes with iodine. (b) Anaaemia. (c) Monckeberg's atherosclerosis.
6. ***Systemic or visceral intoxication*** – is characterised by constipation, furunculosis, urticaria, alopecia and brittle nails.

Investigations

1. *Urine* – Mean 24 hour urinary excretion of fluoride increased (>1.5 ppm).
2. *Radiology* – Osteosclerosis in spine and pelvis (Fig. 20). Beaking and chalky white ground-glass appearance. Calcification of inter-vertebral ligament, sacrospinous and sacrotuberous ligament and of interosseous membrane of forearm.
3. *Blood biochemistry* – (a) Fluoride level in blood >0.27 ppm. (b) Plasma alkaline phosphatase may be elevated.

Management

Preventive – (a) Drinking water should contain 0.5-0.8 ppm of fluorine. Defluoridation of water if high content, or deep bore drinking water. (b) Vitamin C and calcium give protection against toxic effects of fluorides.

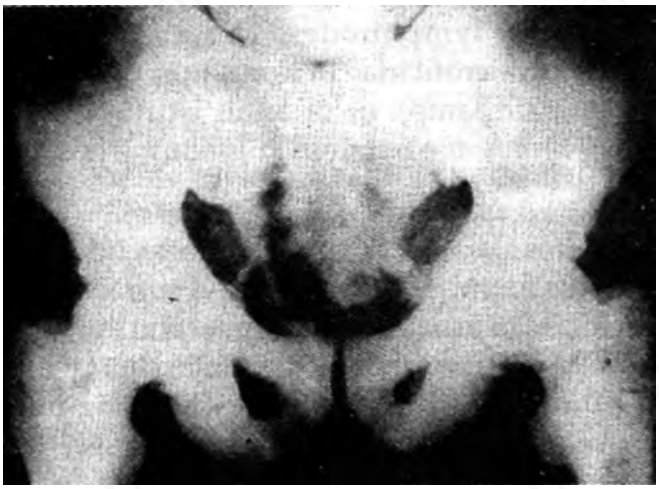


Fig. 20: Milky white appearance of pelvic bones in fluorosis

Of the disease – Avoid seafish, cheese, tea. Do not use toothpastes and other product supplements with fluoride.

CHAPTER 12

Diseases of Children

1. NEWBORN INFANTS

RESUSCITATION OF THE NEWBORN

Asphyxia can occur at birth. Asphyxia is characterized by progressive hypoxia, hypercapnia, hypoperfusion and acidosis. Apnoea occurs when a baby is deprived of oxygen. Continuation of asphyxia leads to stoppage of respiratory movements, fall in heart rate, diminution of neuromuscular tone – *primary apnoea.* In most cases stimulation and exposure to oxygen will induce respiration.

If the asphyxia continues, the baby develops deep gasping respirations, heart rate continues to slow, and it enters a period of *secondary apnoea.* There is now no response to stimulation and respiratory effort will not begin until resuscitation with assisted ventilation and oxygen are initiated without delay.

It must be noted that due to foetal hypoxia, the infant may go through primary apnoea and into secondary apnoea while *in utero.* In both instances the infant is not breathing and the heart rate may be less than 100. The importance is that when faced with an apnoeic infant at birth, it must be considered as a case of secondary apnoea and resuscitation undertaken.

See Table 1 for the equipments and drugs needed for resuscitation.

Indications for resuscitation – The Apgar score is not used in deciding when to initiate resuscitation or deciding the course of action. Plan of action depends on:

- Respiration
- Heart rate
- Colour

Table 1: Equipment and drugs required for resuscitation

Radiant warmer
Suction equipment
• Mucous aspirator
• Meconium aspirator
• Mechanical suction
• Suction catheter, 10 or 12F size
• Feeding tube 8F
• 20 mL syringe
For bag and mask ventilation
• Ambu bag with face masks, newborn and premature sizes
• Oxygen cylinder with flowmeter and tubing
For intubation
• Laryngoscope with straight blades, No. 0 (preterm) and No. 1 (term)
• Endotracheal tubes 2.5, 3, 3.5, 4 mm and stylet
• Scissors and gloves
Drugs
• Epinephrine
• Naloxone hydrochloride
• Sodium bicarbonate
• Volume expanders
• Dopamine
• Sterile water

Resuscitation Procedure: TABCs

T – Maintenance of temperature

- Radiant heat source with an overhead radiant warmer which should be preheated to allow the baby to be placed on a warm mattress.
- Drying the infant with prewarmed towel or blanket.
- Removing the wet linen.

A – Airway

- Positioning. The neonate is placed on its back with the neck slightly extended. A rolled towel can be put under the shoulders to maintain position.
- Suction of mouth and nose of the meconium with mucus aspirator or mechanical suction. The suction pressure should be kept around 80 mm Hg (100 cm water).

Table 2: Medications during resuscitation

Medication	*Indication*	*Dose/route*
Adrenaline (1:10000)	HR zero or < 80 after 30 secs of PPV and CC	0.1 ml–0.3 ml/kg iv, IT
Volume expanders N saline/Ringer's	Bleeding with hypovolemia	10 ml/kg IV Infusion
Naloxone	Resp. depression following narcotic given 4hr before delivery	0.25 ml (0.1 mg/kg) IV
Dopamine	Persistent hypotension	5–20 mcg/min. continuous infusion
Sodium Bicarbonate	Metabolic acidosis Apgar 5 or less at 5 min.	4 mL/kg IV slowly

Table 3: Apgar score

Score	*0*	*1*	*2*
Respiratory effort	None	Slow, irregular	Good crying
Heart rate/min.	Absent	100	100
Colour of body	Blue or pale	Body pink, extremities blue	Pink
Muscle tone	Flaccid	Some flexion	Actively moving the extremities
Reflex stimulation (catheter in nose)	No response	Grimace	Cries, coughs or sneezes

- Clearing the airway of meconium. This is best carried out when the head is delivered. After delivery if the infant is passing thick, particulate meconium, first residual meconium in the hypopharynx should be removed by suctioning through a laryngoscope. This is followed by intubation of the trachea and suctioning of meconium from lower airways, by applying suction directly to an endotracheal tube. After tracheal suctioning, the trachea should be suctioned to prevent aspiration of meconium containing gastric contents into the lung, in case vomiting occurs.

B – Breathing

- If breathing is not spontaneous, provide tactile stimulation by rubbing the baby's back or flicking the soles of the feet.
- PPV if baby remains apnoeic or is gasping in spite of tactile stimulation or respiration is spontaneous but heart rate is < 100/min. (Heart rate is counted by auscultation of the heart or palpating umbilical pulsations for 6 seconds and multiplying the figure by 10).

Bag and mask ventilation – The infant's neck is slightly extended and the mask placed in position and the seal checked by ventilating 2 or 3 times. If chest does not rise look for and correct inadequate seal, blocked airway or inadequate pressure. Ventilate at a rate of 40–60/min. The best indication of successful bag and mask ventilation is an easy rise and fall of the chest.

After 15–30 seconds of ventilation, further action will depend on the heart rate.

> 100: Monitor heart rate, respiration and colour if spontaneous respiration.

If not breathing or gasping: Continue ventilation.

60–100 and increasing: Continue ventilation

60–100 and not increasing: Begin chest compression if heart rate < 80/min. Continue ventilation

< 60: Continue ventilation and chest compressions

C – Maintain Circulation

Chest compressions – are done with thumb or two fingers, applying pressure to the lower third of the sternum. Ventilations are interposed between compressions and a ventilation should follow every third compression. Chest compressions are stopped if the heart rate is 80 beats/min. or more.

If heart rate < 80: Continue chest compression along with bag and mask ventilation, and start medications.

Endotracheal intubation – to ensure open airway.

Indications:

- Prolonged PPV is required
- Bag and mask ventilation is ineffective
- Tracheal suction is necessary
- Suspicion of diaphragmatic hernia.

The tube varies from 2.5–4 depending on infant's weight and gestational age.

Prolonged asphyxia – Therapy only after adrenaline and volume expanders have been given and preceded, accompanied and followed by ventilation.

Apgar score – is a quantitative method for assessing the infant's respiratory, circulatory and neurological status and overall condition of the newborn (Table 3).

SCORE

- 8–10 Normal
- 5–7 Moderately asphyxiated
- < 4 Severe distress

Ideal score at 1 minute is 9. But one minute score is not useful for deciding upon intervention, because action must be initiated before that. A 5 minute score is useful as an objective measure for baby's condition for future reference.

Table 4: Danger signs in the newborn
• Poor feeding
• Cold to touch (hypothermia) or febrile (hyperthermia)
• Inability to suck
• Respiratory distress
• Drowsiness or irritability
• Blue discolouration of lips/tongue
• Convulsion
• Bleeding
• Jaundice in first 24 hours after birth
• Vomiting, abdominal distension
• Umbilical discharge

Timing of the Score

- At first cry
- Once regular respiration is observed
- Delayed if any neurological deficit.

Significance

A low score may indicate:

- Birth asphyxia
- Effect of drug administered to mother during labour
- Intrauterine infection
- Congenital malformations
- Prognostic significance: Serious outlook if score < 4 at 20 minutes

Note: While the Apgar score is not useful for decision-making at the beginning, it is useful for assessing the infant's condition, and the efficacy of resuscitation. Hence, an Apgar score should be done at 1 and 5 minutes of age. When the 5 minute score is < 7, additional score should be obtained every 5 minutes for up to 20 minutes or until two successive scores are 8 or more.

Fallacies

Scoring cannot be used in

- Preterm baby
- Floppy infant
- Infant markedly sedated
- Presence of Erb's palsy
- Does not estimate duration of asphyxia
- Respiration cannot be judged if newborn is on IPPR

Table 5: Cyanosis in newborn
• Congenital heart disease with right-to-left shunt (2As, 5Ts)
Atresia of aorta
Atresia of pulmonary artery
Transposition of great vessels
Tetrad of Fallot
Tricuspid atresia
Total anomalous pulmonary venous drainage
Truncus arteriosus
• Congenital cardiac lesion with CHF
Transposition of great vessels
Aortic atresia
• Pulmonary
Hyaline membrane disease
Pneumonia
Septicaemia
Meconium aspiration syndrome
Transient tachypnoea of newborn
• Neurological
Birth asphyxia
Intracranial hemorrhage
• Haematological
Polycythemia

FIRST CRY OF NEWBORN

Mechanism

- Fall in pulmonary vascular resistance with increase in pulmonary blood flow
- Increased venous return to LA with increase in LA pressure and functional closure of foramen ovale
- Increase in arterial oxygen tension causing functional closure of ductus arteriosus

Significance of first cry – During intrauterine existence, foetal lungs are non-functional because the foetus derives its oxygen needs from the placental circulation. During normal vaginal delivery, there is compression on the foetal thorax in the birth canal and the fluid present in the alveoli, a one-third of which is emptied out of the lungs.

With the first cry of the newborn, a high inspiratory pressure is created, which forces the remaining lung fluid into the lymphatics from where it is absorbed and the lungs begin to function on their own for the first time.

Table 6: Causes of a weak cry
• Caesarean section.
• Precipitate labour.
• Intrauterine hypoxia.
• Inability to initiate respiration due to congenital cerebral abnormality.
• Prematurity
• Hyaline membrane disease

Table 8: Diagnostic criteria for asphyxia neonatorum
• Signs of foetal distress
• Acute metabolic acidosis
• Apgar score at 5 minutes < 5
• Initiation of respiration > 5 minutes
• Features of ischemic hypoxic encephalopathy
• Multiorgan damage
Note: Any four of the above

Causes of a weak cry – If the pressure required to force the fluid out of the foetal lung is not sufficient there is transient tachypnoea (Table 6).

2. DISEASES OF THE NEWBORN

RESPIRATORY DISTRESS IN THE NEWBORN

Asphyxia Neonatorum

Asphyxia neonatorum is a state of anoxia as a result of lack of oxygen and/or deficiency of perfusion to various organs arising from absence of normal respiratory function at birth.

Aetiology

- Persistence of intrauterine hypoxia (major cause)
- Placental: Functional failure of placenta to function as respiratory organ, e.g. inefficient uteroplacental circulation, early separation of placenta, small size of placenta or its infarction, circumvallate placenta
- Maternal hypoxic states: Anemia, eclampsia, cardiac disease, severe bronchial asthma, hypotension

Table 7: Clinical features asphyxia neonatorum
CNS
• Hypoxic ischemic damage (cortical infarcts, damage to thalamus/basal ganglia)
• Signs of increased intracranial tension
Renal
• Acute tubular necrosis
• ADH syndrome
GI
• Necrotising enterocolitis
• Liver damage
Cardiac
• Transient myocardial ischemia
• MR, TR
Lung: Haemorrhage, oedema, respiratory distress syndrome, meconium aspiration
Haematological: DIC

Table 9: Factors of poor prognosis
• Prolonged duration and severe asphyxia
• Seizures
• Raised intracranial pressure
• Persistent oliguria
• CT brain shows hypodensities

- Neonatal injury: Prolonged head compression, abnormal lie such as breech or oblique causing increased intracranial pressure and thus asphyxia
- Medications to mother (prenatal and intranatal, e.g. anaesthetic agents, sedatives) depress respiratory centres of the newborn, resulting in continuation of intrauterine asphyxia

Clinical features, diagnostic criteria and prognostic factors of asphyxia neonatorum are given in Tables 7, 8 and 9, respectively.

Management

- IV fluids
- Warmth
- Management of cerebral oedema
- Symptomatic treatment of seizures, hypoglycemia, hypocalcemia
- Cerebral cooling

(See Resuscitation in Newborn)

HYALINE MEMBRANE DISEASE IN THE NEWBORN

Predisposing Factors

It is one of the major causes of death in the newborn period. Incidence inversely proportional to gestational age and weight. Common in premature infants of diabetic mothers delivered before term, Caesarean section, asphyxia, precipitous delivery, after antepartum haemorrhage.

Pathophysiology

(1) Surfactant (dipalmitoylphosphatidylcholine) deficiency leads to collapse owing to increased surface tension, so there is a failure to maintain functional residual capacity. Surfactant synthesis by Type II alveolar cells increases with foetal maturity. (2) Small alveoli – Diameters of airways up to bronchioles are smaller in prematures, requiring greater force for inflation and larger transpulmonary pressure to keep them from deflating. (3) Weakened compliant chest wall at this time compounds tendency to atelectasis, offering poor resistance.

These factors produce near-atelectasis, dyspnoea and tachypnoea, increased airway resistance and work of breathing, and eventually hypoxia, hypercapnia and acidosis. These events give rise to pulmonary vasoconstriction, maintenance of ductal blood flow and foramen ovale flow in an attempt to perfuse the lungs. Decreased lung flow causes ischemic necrosis of surfactant cells and the vasculature causing effusion of protein-like material into alveolar spaces, producing the hyaline membrane.

Lungs appear liver-like. Microscopically there is extensive atelectasis, engorgement of vessels and lining of alveoli by acidophilic homogenous membrane; membranes are seen only 6–8 hours after birth.

Clinical Features

Signs appear minutes after birth; may require resuscitation. Late tachypnoea is very unusual.

- Rapid shallow respirations increasing to 60 or more per minute.
- Audible grunting (ominous sign).
- Intercostal and subcostal retractions.
- Nasal flare.
- Duskiness with increasing cyanosis poorly responsive to oxygen.
- Breath sounds normal or diminished with harsh, tubular quality, fine crepitations on deep inspiration at lung bases.

Worsening is characterised by increased dyspnoea, air hunger, progressive cyanosis, decrease and then absence of grunting, absent breath sounds despite chest movement, hypothermia, hypotension, irregular breathing, acidosis and apnoea; progresses to death in a few hours. Death is rare after 3 days if an infant survives severity of newborn respiratory distress judged by Anderson and Silverman's score.

Complications

Of the disease

- Hypoxia, hypercapnia, acidosis, respiratory failure.
- Persistence of ductus arteriosus – delayed closure due to hypoxia, acidosis, increased pulmonary pressure, immaturity of the infant and local release of ductal dilators such as prostaglandin E_2 and E_2 causes persistent apnoea, systolic or continuous murmur, increases oxygen dependency, aggravates hypercapnia, cardiomegaly and cardiac failure.
- Intraventricular and pulmonary haemorrhage.

Of intensive care

- Tracheal intubation – Obstruction of tube, cardiac arrest during suction, bleeding and ulceration of nose and throat from trauma, vocal cord avulsion, subglottic stenosis, laryngeal oedema and stridor.
- Umbilical catheterization – Vascular embolism, thrombosis, perforation, ischemic necrosis of viscera, gangrene of legs, haemorrhage after removal of heparinised catheter.
- Oxygen toxicity – Retrolental fibroplasia, bronchopulmonary dysplasia.
- Pneumothorax and pneumoperitoneum (with intubation, respirator)
- Secondary infection.
- Anemia due to frequent blood collections.

Diagnosis

1. Low pO_2 < 50 mm Hg, pCO_2 > 50 mm Hg and acidosis signal respiratory failure.
2. Radiograph chest – Fine reticular granularity of lung fields with air bronchogram seen within 6–12 hours characteristic but not pathognomonic.

OTHER CAUSES OF NEONATAL RESPIRATORY DISTRESS

a. *Respiratory* – 1. Prenatal, natal meconium aspiration. 2. Intrauterine or postnatal pneumonia, esp. group B streptococcal pneumonia. 3. Pneumothorax,

Table 10: Anderson and Silverman's score

Upper chest	*Lower chest retraction*	*Xiphoid retraction*	*Alae nasi flare*	*Expiratory grunt*
Gr 0 Synchronised motion	None	None	None	None
Gr 1 Insp. lag	Just visible	Minimal	Minimal	With stetho.
Gr 2 "See-saw" movement	Marked	Marked	Marked	Naked ear

Grade 0–1 for each criterion indicates no distress.
Grade 2 for each criterion indicates severe distress. Applicable 1–2 hours after birth.

pneumomediastinum. 4. Pulmonary haemorrhage. 5. Transient tachypnoea of the full-term newborn (persistence of lung fluid, recovers fully). 6. Wilson-Mikity syndrome (late onset dyspnoea, X-ray shows 'bubbly' lungs, cause unknown). 7. Congenital malformations–Choanal atresia, Pierre Robin syndrome (small chin, cleft palate, tendency for tongue to fall back); laryngeal webs, stenosis, atresia, vascular rings, ectopic goitre, T-O fistula, congenital lobar emphysema, pulmonary agenesis, diaphragmatic hernia, congenital tumours, e.g. cysts, teratomas.

b. *Cardiovascular* – CHF from any cause, congenital heart disease PDA, coarctation of aorta, cyanotic heart disease, severe anemia, polycythemia, myocarditis, arrhythmias, diabetic offspring.

c. *Neurological* – Birth asphyxia or injury, intracranial haemorrhage, plexus injuries in breech deliveries, meningitis.

d. *Metabolic* – Acidosis, uraemia, inborn errors of metabolism (hyperammonaemia), hypoglycemia, hypothermia.

Anderson and Silverman's score for newborn respiratory distress: See Table 10.

Management

Course can be altered by intensive care and supportive therapy.

1. *Treatment of inadequate gas exchange* – Warm humidified oxygen to keep arterial blood levels from 50 to 70 mm Hg with stable vital signs, while minimising risks of toxicity. Inspired concentration safely kept at 40–70%. If > 50 mm Hg O_2 cannot be achieved, use of continuous positive airway pressure (CPAP) by nasal prongs or head box is used. Persistent apnoea, blood pH < 7.2, pCO_2 > 60 mm Hg, pO_2 < 50 mm Hg, at O_2 concentrations of 70–100% need assisted ventilation (mask and bag resuscitator or variable pressure respirator with endotracheal tube). This may also help in correction of respiratory acidosis.
2. *Correction of metabolic acidosis* – Sodium bicarbonate 7.5% solution 2 mL/kg slowly IV diluted in 5 times volume of 5% glucose (1 mL $NaHCO_3$ = 0.9 mEq Na). Formula – HCO_3 [mEq needed = Deficit of HCO_3 × 0.6 × body weight (kg)]. One half of calculated amount given initially. More than 12 mEq/kg/day can aggravate hypernatremia and CHF. Alternatively, THAM 1 mL/kg for each pH unit below 7.4 at rate of 1 mL/min.
3. *Pharmacological closure of ductus* – If ductus complicates the disease, oral or rectal indomethacin 0.2 mg/kg given thrice at 12 hour intervals. The drug inhibits prostaglandin synthesis. Surgical closure may be necessary. Frusemide 1–2 mg/kg IM/IV and Digitalis 0.02 mg/kg digitalising dose if CHF occurs.
4. *Antibiotics* – because of frequency of superinfection Ampicillin 200 mg/kg IV 12-hourly with gentamicin 5 mg/kg IV 12-hourly, or Amikacin 15 mg/kg IV 12-hourly.
5. *Exchange transfusion* – may benefit by improving oxygen carrying capacity of blood.
6. Steroids are ineffective and contraindicated.
7. *General measures* – Prevention and treatment of hypothermia and hypoglycemia, IV fluids not more than 80–100 mL/kg/24 hours. Parenteral nutrition if available. Incubator care. Gentle and minimal handling. Inj. vitamin K 1 mg to prevent haemorrhage IV. Phenobarbitone 20 mg/kg to prevent intra-ventricular haemorrhage. Monitoring of pulse, temperature, respiration, CVP, PaO_2, blood pH, blood HCO_3, Hb, less often serum electrolytes, and blood glucose, ECG.
8. *Use of artificial surfactant* – 2 varieties available – (i) Bovine (Survanta). (ii) Synthetic (Exosurf). Saline suspension 10 ml intratracheally within first day rapidly reduces oxygen requirement. A single dose produces transient benefit in oxygenation and reduces need for ventilation. Multiple doses may improve prognosis when given within the first 2 days every 12 hrs for 4 doses (rescue therapy).

Prevention

1. Prevention of prematurity, unnecessary and poorly timed LSCS, management of high risk pregnancy and labour.
2. Assessment of foetal maturity. Foetal head circumference by ultrasound. 'shake test' with amniotic fluid and 1: 2 dilution of 95% ethanol producing complete ring of bubbles at meniscus indicating foetal lung maturity, or determination of amniotic fluid lecithin to sphingomyelin ratio which is 2: 1 by 35 weeks gestation, increasing till term.

3. Antenatal administration to mother, of synthetic steroids in absence of toxaemia, diabetes or renal disease, 24 to 72 hours prior to delivery of foetus at 32 weeks gestation reduces incidence of and mortality from hyaline membrane disease. One or two doses of 6 mg betamethasone acetate and 6 mg of betamethasone phosphate IM.

Croup: It is characterized by acute onset of hoarseness of voice, inspiratory stridor, barking cough and some degree of respiratory distress. It usually occurs due to viral (parainfluenza, RSV), acute laryngotracheobronchitis. There may be mild fever. Chest X-ray reveals subglottic narrowing resembling a Church spire (steeple or pencil point sign). Lateral view of neck shows ill-defined thumb-shaped opacification at site of epiglottitis (Thumb sign). *Treatment:* (a) Nebulised budesonide, corticosteroids. (b) Supportive measures like humidified O_2, or inhalation of mixture of helium and O_2.

INFECTIONS OF THE NEWBORN

Neonates, particularly those born prematurely, are relatively immunocompromised and are, therefore, prone to more infections, more severe disease and infection with unusual organisms. Almost all foetal infections and a significant proportion of those in the neonatal period are caused by organisms acquired from the mother; that is, they are vertically transmitted. Transmissions may be transplacental *in utero*, perinatal during the birth process or post-natal (including transmission via breastfeeding). Neonates also acquire infections horizontally including nosocomial. Several infections including HIV, may be transmitted by more than one of these routes, but because diagnosis and management differ between routes, it is convenient to consider transplacental infections separately from perinatal and postnatal infection.

Transplacental infections of the foetus. Most infections affecting women during pregnancy remain localized (e.g. to GI or respiratory tract). However, if blood stream infection occurs, the foetus may be infected transplacentally.

Clinical Features

Placentitis can occur without infection of the foetus (e.g. tuberculosis, malaria, syphilis, CMV, rubella), but may cause foetal growth retardation. Even in absence of foetal and placental infection, the foetus can be affected indirectly by fever, anoxia, circulating toxins and metabolic derangement. When an embryo or foetus is infected, possible outcome are:

a. *Embryonic death and resorption.*

b. *Abortion and stillbirth.*

c. *Developmental anomalies and teratogenesis* – CMV, rubella and VZV cause developmental anomalies that appear to result at least partly from the ability of these viruses to cause cell death, changes in cell growth and chromosomal damage. In contrast, inflammation and tissue damage appear to be responsible for structural abnormalities caused by congenital syphilis, HSV infection and toxoplasmosis.

d. *Intrauterine growth retardation* may be a marked feature of foetal and placental infection. Typically, it affects both head and general growth. Most herpes viruses, protozoal infections and rubella can cause this.

e. *Asymptomatic infection* – When pregnancy progresses to term, most infants with transplacental infection are asymptomatic at birth. However, these children may develop late sequelae, sometimes after years; examples include interstitial keratitis after congenital syphilis, chorioretinitis in toxoplasmosis and late-onset hearing loss in CMV disease.

f. *Congenital disease*, e.g. rubella, CMV. Symptoms manifest at or soon after birth and consist of growth retardation, congenital defects and inflammatory features including jaundice, hepatosplenomegaly, pneumonia and purpura. The inflammatory symptoms may be self-limiting if controlled by neonatal defence mechanisms, or may progress and result in early death.

Persistent postnatal infection – Certain microbial agents may continue to survive and replicate for years after *in utero* infection. Rubella, CMV, HSV, HIV, syphilis, toxoplasmosis, tuberculosis and malaria can all cause progressive or late-onset disease.

Diagnosis

Tests on the mother – Identification of mothers who are chronically infected with HIV, hepatitis B or C virus, or syphilis can be achieved by prenatal or ideally pre-conceptual serological testing. Serological testing is also used to detect pre-existing immunity (e.g. to rubella), which identifies at risk pregnancies and provides baseline for subsequent serological determination of *in utero* infection should the mother be exposed.

Tests in the foetus (e.g. foetal blood sampling, amniocentesis) are performed only in situations in which there is a high risk of foetal damage and confirmation of foetal infection is likely to result in termination of pregnancy (e.g. in first-trimester rubella), PCR-based tests are used for detection of microbial nucleic acid in blood or amniotic fluid.

Postnatal tests – Detection of organism by culture or by molecular diagnostic methods allows specific and rapid diagnosis. Examples include culture of rubella or CMV from urine sample collected within the first 21 days after birth, which confirms congenital infection, and PCR analysis to diagnose vertically acquired HIV infection (though it should be remembered that false-negative results may occur in first 2 months). Serological tests are sometimes necessary. If IgG titre in an infant is fourfold or greater than that of the mother, a titre that rises over time in the infant, or failure of disappearance of maternal IgG by 12 months is highly suggestive of infection.

Management and prevention – Immunization against rubella is highly successful. Routine antenatal care should detect mothers with chronic infections (e.g. TB, malaria, syphilis) and treatment can restore both the mother's health and protect the foetus. In other cases, asymptomatic infection can be detected in pregnancy on blood tests allowing strategies to protect the foetus (e.g. neonatal hepatitis B prophylaxis, antiretroviral drugs to reduce transmission of HIV).

Perinatal and postnatal infections of the neonate

There are three possible mechanisms by which perinatal transmission of infection can occur:

- Physiological changes before and during labour may promote passage of maternal blood to the foetus, thus transmitting blood borne infection, such as HIV and hepatitis B.
- Ascending infection from the vagina can cause chorioamnionitis and foetal infection. This may occur following rupture of amniotic membranes or invasion of intact membrane by certain organisms (e.g. group B *Streptococcus*).
- Passage through the birth canal exposes the infant directly to maternal blood and vaginal secretions.

Neonatal sepsis. Incidence of infection and sepsis in premature infants is 3–10 fold greater than in full-term infants of normal weight. Other risk factors for neonatal sepsis at any gestation include prolonged (> 18 hours) rupture of amniotic membranes before delivery, chorioamnionitis and UTI in the mother. Neonatal sepsis can be classified into:

Early-onset sepsis manifests at birth or within 48 hours. The causative organisms are always maternally derived; group B *Streptococcus* and *E. coli* are predominant. The disease often has a fulminating course; pneumonia and septicemic features predominate.

Late-onset sepsis (commencing after 48 hours) is usually caused by organisms from the environment and only occasionally by maternal flora. The onset is often insidious and there is greater likelihood of focal infection, including meningitis and osteoarticular infection. There is a wide range of causative organisms – coagulase-negative staphylococci, Gram-positive cocci, Gram-negative enteric bacilli and fungi.

See Table 11 for the clinical features of neonatal sepsis.

Table 11: Clinical features of neonatal sepsis

Early-onset
• Maternal risk factors
• Unexplained birth asphyxia
• Respiratory distress (radiographic appearance of pneumonia may be indistinguishable from that of hyaline membrane disease)
• Poor circulatory status (low BP, cold peripheries)
• Unexplained neutropenia (neutrophil count < 100/mm^3)
• Unexplained hypoglycemia
• Rash (consider Listeria)
• Hepatosplenomegaly
• Jaundice
Late-onset
• Bradycardia and apnoea
• Poor feeding, vomiting/increasing gastric aspirates/abdominal distension
• Irritability
• Convulsions
• Increasing jaundice
• Increasing respiratory distress and ventilatory requirements
• Unexplained rapid changes in neutrophil and/or platelet counts
• Signs of focal inflammation/infection

Investigations

Early-onset Sepsis

Blood culture – A minimum of 0.5 mL per blood culture bottle.

Deep-ear culture – Samples collected through a sterile ear speculum, if taken within first 6 hours, should reflect amniotic fluid uninfluenced by passage through the birth canal. This can help confirm the type (if any) of bacteria present in the amniotic fluid before delivery. It may aid the choice of antibiotics when culture results become available.

Maternal cultures – Blood cultures, and placental and high vaginal swabs.

Chest radiograph – for pneumonia and other lung pathology.

Lumbar puncture – CSF for microscopy and culture performed after infant is clinically stable.

Viral serology and PCR analysis – for HSV and enteroviruses if clinically suspected.

Late-onset sepsis – As for early-onset sepsis. In addition, examination of urine (by clean catch methods) and cultures from any indwelling devices, such as endotracheal tube and vascular catheters.

Management

Early-onset sepsis – Intensive care. Combination of benzylpenicillin and gentamicin is the best choice. In non-intensive care setting, cefotaxime can be used as a single agent. When infection with *Listeria monocytogenes* is suspected, ampicillin instead of penicillin or in addition to cefotaxime.

Late-onset sepsis – In ICU, a broad spectrum combination such as Ciprofloxacin and an aminoglycoside should be first-line therapy. In non-ICU setting, combination of ampicillin and cefotaxime. Duration of treatment depends on clinical response but minimum period is 10 days.

General supportive care includes ventilatory support, careful fluid management and circulatory and blood product support. Parenteral nutrition may be required (as in necrotizing enterocolitis).

Fungal infection is most commonly caused by *Candida spp.* Treatment should be commenced with amphotericin, and 5-flucytosine added when CNS, renal or osteoarticular involvement is suspected.

SEPSIS AND MENINGITIS

Common organisms – Gram negatives, group B streptococcus, Staph. aureus.

Symptoms and Signs of septicaemia and convulsions. Bulging fontanelle and neck stiffness may be absent in 75% of cases. Initially may not 'do well' or just 'feed poorly'.

Diagnosis: CSF examination and culture. Other site cultures and blood culture may help. Normal CSF protein as high as 45–100 mg/dL in term baby and up to 120 mg/dl in preterm. Up to 7 cells/μL with 50–60% neutrophils. Up to 800 RBCs/cmm normal in newborn and up to 50 in first 7 days. CSF sugar < 50% of blood sugar diagnostic of meningitis.

Complications: Ventriculitis, status epilepticus, neural deficits, deafness, hydrocephalus, blindness, abnormal speech and learning problems later.

Management: *Antibiotics* – Ampicillin 100 mg/kg IV under 7 days, and 200 mg/kg/day in 4 divided doses after 7 days of life, with Gentamicin 7.5 mg/kg/day in two divided doses IV. Must be given for at least 10–14 days or 5–7 days after clinical response in case of sepsis, and at least 21 days treatment for meningitis. Amikacin 15–20 mg/kg IV 12-hourly. (Effective in most infections except pseudomonas). Cefotaxime 100 mg/kg/day IV. Cefotaxime and Amikacin combination works in most cases.

For group B streptococcus – Aqueous penicillin G 100,000 U/kg/day IV 12-hourly if under 7 days, 250,000 U/kg/day in 8-hourly doses after 7 days.

Staphylococcus – Cloxacillin up to 200 mg/kg/day IV in 8-hourly or 6-hourly doses. Vancomycin 15 mg/kg 8–12 hrly for resistant cases.

Pseudomonas – Combination of Gentamicin with Carbenicillin up to 400 mg/kg/day IV in 6-hourly doses or Ceftazidime 100 mg/kg 8 hourly or Piperacillin 100 mg/kg IV 12 hourly.

Candidiasis – Amphotericin B 0.7–1-mg/day for 3–4 weeks or Fluconazole 3–6 mg/kg/day IV 12 hourly.

For ventriculitis – Gentamicin 2.5 mg intraventrically daily till ventricular fluid sterile in poorly responding patients or Amikacin 5 mg, 2–3 times a week as last resort. CT scan is indicated.

Supportive treatment – For convulsions diazepam 0.2–0.3 mg/kg IV slowly. Restricted IV fluids, blood transfusion. Relief of raised intracranial tension may be necessary. Exchange transfusions have been tried.

UMBILICAL INFECTION (OMPHALITIS)

Causes – Any pyogenic bacteria commonly Staph. aureus. Danger of haematogenous spread or extension to liver and peritoneum. Foul smelling umbilical discharge or failure of cord to separate within normal period of time may provide a clue. General symptoms and signs might be minimal.

Treatment – Appropriate systemic antibiotics. Local application of spirit.

Prevention – Clean cord care. Thrice daily swabbing with spirit or application of triple dye. The cord is best left open, no restrictive binders are necessary.

Viral infections – can be transmitted perinatally through the placenta during labour or directly via blood and secretions swallowed by the infant during delivery.

HSV – Caesarean section within 4 hours of rupture of the membrane reduces risk of transmission. In babies born of a mother with active lesions, IV acyclovir (if swabs from nose, eyes and skin are positive) or baby develops signs of infection.

VZV – Infants at greatest risk are those born to mothers who develop chickenpox within 7 days before or after delivery.

Varicella-zoster – Immunoglobulin is given and acyclovir started at first sign of the disease in the infant.

CMV – Postnatally acquired disease seldom requires treatment except in the immuno-compromised. Children with symptomatic congenital infection may benefit from a 6-week course of IV ganciclovir.

Enteroviruses can cause multisystem involvement in the newborn. Immunoglobulin IV may be helpful.

Hepatitis B is mainly transmitted postnatally. Maternal antenatal screening should identify at-risk pregnancies and prophylaxis with immunization is necessary.

Human papillomavirus causes genital warts. It may be transmitted at birth, and can cause perianal warts in the infant, or occasionally juvenile laryngeal papillomatosis years later.

HIV infection occurs mainly around time of labour or subsequently through breastfeeding. Antiretroviral treatment during short term protocols have been evolved for the developing countries. Pregnancy reduce risk of transmission. The risk might be reduced by avoidance of very prolonged breastfeeding and avoiding subclinical mastitis in the mother.

Short-term Protocols

1. AZT given to pregnant women in the dose of 100 mg 5 times a day from 35 weeks of gestation till delivery followed by IV administration of AZT during labour. AZT is also given to the newborn baby in dose of 2 mg/kg 4 times or day for 6 weeks along with replacement feeding.

   This regimen reduces transmission rates by 65%.
2. Second regimen is a single dose of nevirapine 200 mg given to mother at the onset of labour and a single dose of nevirapine in dose of 2 mg/kg given to baby within 48 hrs of birth. This regimen reduces transmission by 50%. This protocol is simple, inexpensive, effective and feasible in our country and adopted as National Policy in India.

Safe delivery: Elective LSCS reduces transmission by decreasing the contact of the baby with infected maternal secretions.

JAUNDICE IN NEWBORN

Aetiology

Normal bilirubin metabolism requires the following factors – (i) Maturity of liver. (ii) Normal load of bilirubin. (iii) Adequate quality and quantity of glucuronic acid conjugate for conversion of lipid-soluble (indirect) bilirubin to water-soluble (direct) bilirubin for proper excretion. (iv) Normal biliary passages. (v) Patency and motility of intestines.

It is only indirect bilirubin that crosses the immature blood brain barrier causing kernicterus or brain damage.

Varieties

1. *Immature liver* – (a) Jaundice of prematurity. (b) Physiological jaundice.
2. *Increased load of bilirubin* – (a) Rh incompatibility. (b) ABO incompatibility. (c) Hereditary spherocytosis. (d) Glucose-6-phosphate dehydrogenase deficiency. (e) Enclosed haemorrhage cephalhaematoma. (f) Infants of diabetic mother (polycythemia). (g) Polycythemia (SFD). (h) Increased free bilirubin – Decreased serum albumin as in prematurity and neonatal sepsis. (i) Bilirubin displacement from albumin by drugs like sulphonamides, sodium benzoate, injectable diazepam.
3. *Enzyme abnormality* (glucuronyl transferase) – (a) Reduced activity – anoxia, infection, hypothermia, hypothyroidism. (b) Blocking of enzyme action – drugs like vitamin K analogues. (c) Absence or decreased quantity – (i) Genetic type (Crigler-Najjar syndrome). (ii) Prematurity.
4. *Obstructive jaundice* – (i) Intrauterine and neonatal viral infections causing hepatitis. (ii) Congenital atresia of bile ducts. (iii) Choledochal cyst. (iv) Inspissated bile syndrome. (v) Metabolic diseases like galactosaemia, tyrosinaemia. In all these, direct bilirubin is more than 15% of the total.
5. *Other causes* – Congenital familial non-haemolytic jaundice. Breast milk jaundice. Hypertrophic pyloric stenosis.

Clinical Manifestations

1. ***Physiological jaundice*** – Occurs in about 50% of infants. Appears on about the 4th day and lasts from a few hours to 7 days. Usually not above 12 mg%. Breast-fed babies can have a high level up to 16 mg% which does not require intervention. Stools retain bile pigment. Table 12 gives factors causing exaggeration of physiological jaundice

Clinical Features

Phase 1 – Jaundice appears on about 4th day, and lasts for 5 days in term infants and about 7 days in preterm infants, when there is rapid rise in serum bilirubin to 12 and 15 mg% respectively.

Table 12: Factors causing exaggeration of physiological jaundice

Factor	*Association*
Bilirubin load on liver	Polycythemia, diabetic mother, delayed cord clamping, extravasated blood, intraventricular haemorrhage
Defective uptake from plasma	Decreased Y protein from caloric deprivation
Defective bilirubin conjugation	Due to decreased UDPG activity, e.g. inhibitors in breast milk, hypothyroidism
Decreased hepatic excretion	Congenital infections
Inadequate hepatic perfusion	Hypoxia, congenital heart disease
Increased enterohepatic circulation	Unfed babies, delayed passage of meconium

Table 13: Mechanisms of jaundice

• Increased bilirubin load on liver
Raised erythrocyte volume
Increased enterohepatic circulation of bilirubin
• Decreased erythrocyte survival
Defective uptake of bilirubin from plasma
Decreased ligandin (Y protein)
Increased binding of Y protein by other anions
Decreased hepatic uptake
• Defective bilirubin conjugation
Decreased UDPG activity
Defective bilirubin excretion

Table 14: Causes of jaundice

Increased production
• Rh, ABO incompatibility
• Hereditary spherocytosis
• Non-spherocytic hemolytic anemia: G-6-PD or pyruvate kinase deficiency
• α-thalassemia, vitamin K3-induced haemolysis
• Sepsis
• Increased enterohepatic circulation: pyloric stenosis, large bowel obstruction
Decreased clearance
• Inborn errors of metabolism: Crigler-Najjar syndrome (type I, II)
• Drugs and hormones: Hypothyroidism, breast milk jaundice

Phase 2–A decline to about 2 mg% occurs which lasts for up to 14 days after which normal values are reached. This phase may last for more than one month in preterm infants and those with exclusive breastfeeding. Tables 13 and 14 give mechanism and causes of jaundice in newborn.

2. ***Pathological jaundice***

Features of pathological hyperbilirubinemia:

- Jaundice in first 24 hrs
- Increase in total bilirubin > 0.5 mg/dL/hr or 5 mg/dL/24 hrs.
- Total bilirubin > 15 mg/dL
- Direct bilirubin > 2 mg/dL

Neonatal jaundice of prematurity – is more marked and more prolonged than in full-term infants owing to glucuronyl-transferase deficiency. In the absence of *Rhesus* or ABO incompatibility, this may result from injudicious use of vitamin K analogues, or sulphonamides in premature infants. Jaundice of prematurity is aggravated by birth asphyxia and sepsis.

3. ***Haemolytic disease of the newborn*** –

(a) **Due to ABO incompatibility** – Development of jaundice within first 24 hours (before one expects physiological jaundice to become manifest). Serum bilirubin level exceeds 12 mg/100 mL in first 24 hours. No anemia, liver and spleen do not enlarge. Jaundice disappears in 3–7 days. Rarely the disease assumes greater severity, there is more severe jaundice, anemia and hepatosplenomegaly.

(b) **Due to Rh-incompatibility** – Jaundice is present from birth or appears within 48 hours. Associated anemia, enlargement of liver and spleen. Severe anemia at birth can cause foetal anasarca (hydrops). Increasing drowsiness, restlessness, head retraction, twitchings and convulsions may develop and indicate kernicterus, the most serious complication due to destruction of basal ganglia, usually fatal in the acute stages. Bile pigments in urine and marked increase of nucleated red cells in circulation.

(c) **Haemolytic jaundice due to congenitally abnormal erythrocytes** (Hereditary spherocytosis) – When much blood is lysed jaundice may become intense, this depends on intensity of haemolysis and immaturity of liver.

4. ***Obstructive jaundice*** – *Congenital atresia of bile ducts* – Jaundice appears 7–10 days after birth and gets progressively worse. Stools clay coloured and urine dark containing bile salts and pigments. Gradual enlargement of liver and spleen, mild anemia. Haemorrhages may occur into the skin or from stomach or intestine. Fatal within 3 to 8 months.

5. ***Other causes:***

(a) **Jaundice due to infections** – Septicaemia usually from pyogenic umbilical infection, congenital

Table 15: The congenital hyperbilirubinaemias

	Type			
Feature	*Najjar and Crigler*	*Dubin Johnson*	*Gilbert*	*Rotor*
Familial	–	+	+	+
Severity	+++ (fatal)	+	+	+
Age-group	Infancy	Any	Any	Any
	(usually first noted in childhood)			
Type of bilirubin in serum	Unconjugated	Conjugated	Unconjugated	Conjugated
Bile in urine	No	+	No	+
Histology of liver	Normal	Blackish pigment present	Normal	Normal, same condition as Dubin-Johnson but without pigment
				Bromsulphthalein retention↑
				Non-filling gallbladder
Other abnormalities	Kernicterus	Bromsulphthalein retention↑		
		Non-filling gall-bladder. Alkaline phosphatase↑		

syphilis, generalized herpes simplex infection. Toxoplasmosis and cytomegalic inclusion disease.

(b) **Congenital hyperbilirubinemia** – of the four forms only Najjar-Crigler courses severe jaundice and has a poor prognosis. *Crigler-Najjar syndrome* – (i) Type I is rare and due to complete absence of hepatic glucuronyl transferase activity. Severe hyperbilirubinemia develops within first 3 days. Treatment is repeated exchange transfusions and phototherapy. Kernicterus and death occurs in half the infants. (ii) Type II disease is more common and benign. Bilirubin levels seldom > 20 mg/dL and kernicterus is rare. It responds to oral phenobarbitone (Table 15).

(c) **Benign recurrent intrahepatic cholestasis (BRIC)** – Rare familial AR disorder with recurrent attacks of pruritus and jaundice. Episodes can occur at any age. Conjugated bilirubin and alkaline phosphatase raised, benign disorder and does not lead to end stage liver disease.

(d) **Progressive familial intrahepatic cholestasis (FIC)** – The name is applied to three related syndromes. Type I presents in early infancy as cholestasis and progresses to malnutrition, growth retardation and end-stage liver disease during childhood both FIC 2 and FIC 3 have been described. FIC 3 has high serum levels of γ-glutamyl transferase activity.

(e) **Hypothyroidism** – Persistent elevation of indirect bilirubin is the first sign of congenital hypothyroidism in neonates. It is due to decreased activity of UDPG for weeks or months after birth. Administration of thyroxine clears the icterus.

SEQUELAE OF UNCONJUGATED HYPERBILIRUBINEMIA

Transient encephalopathy – Suspected by increasing lethargy with rising bilirubin levels. Recovery with exchange transfusion.

Kernicterus (bilirubin encephalopathy) – It is a symptom-complex which results from the fixation of indirect bilirubin to basal ganglia in the brain and other important brainstem nuclei (nuclear staining), notably the cochlear nucleus. It usually occurs when indirect serum bilirubin of more than 20 mg persists for more than 24 hours, but can occur at a lower level in premature babies, hypoxia, and sepsis.

The neurotoxicity depends on the maturity of the newborn and concentration of unbound bilirubin which can cross the blood-brain barrier especially when the level of bilirubin is very high (> 20 mg/dL) and persists for > 24 hours in the first 4 to 5 days of life.

Bilirubin encephalopathy is rare beyond 5–7 days of life as the blood brain barrier (BBB) matures with age and becomes virtually impermeable to unconjugated bilirubin.

Clinical Manifestations

- Appears between 2nd and 6th day
- Lethargy, refusal of feeds, shrill cry
- Bulging fontanelle, 'setting sun' sign, opisthotonic fit and later generalized convulsions, poor reflexes

Clinical Stages

I. Hypotonia, dampened Moro's reflex, depressed sensorium, vomiting, high-pitched cry

II. Hypertonia progressing to opisthotonus, seizures, fever, oculogyric crisis

III. High-pitched cry, convulsions, death.

Late Sequelae

- Sensorineural deafness
- Cerebral palsy (spastic, athetoid)
- Paralysis of upward gaze
- Mental retardation
- Epilepsy
- Dental dysplasia and brownish staining

Investigation of a Case of Neonatal Jaundice

Aim is to distinguish physiological from pathological jaundice.

History

About neonate

- Time of onset
- Increasing/decreasing
- Colour of urine and stool
- General factors: Feeding difficulties, sepsis if any, breastfeeding or not
- Delivery: Preterm, any drugs, blood transfusion

Maternal

- Previous babies with jaundice or needing exchange transfusion
- Illness suggestive of viral infection
- Drugs, e.g. sulphonamides or antimalarials causing haemolysis in G-6PD deficiency

Family history

- Of jaundice and anemia
- Of neonatal or early infant death due to liver dysfunction suggesting galactosaemia, Crigler-Najjar syndrome or a 1- antitrypsin deficiency

Examination: Signs suggestive of non-physiological jaundice:

- Intrauterine growth retardation
- Stigmata of intrauterine infections, e.g. microcephaly, cataracts, hepatosplenomegaly, chorioretinitis, etc.
- Cephalhaematoma, bruising, signs of intraventricular hemorrhage

Clinical estimation of jaundice – The icterus is first noticed in the face and as the bilirubin level rises, it proceeds to the trunk and extremities.

Table 16: Correlation of dermal zones and levels of bilirubin

Dermal zone	*Bilirubin (mg/dl)*
Face	5
Upper trunk	10
Lower trunk	12
Extremities	15
Palms and soles	> 15

Correlation of dermal zones and levels of bilirubin see Table 16

Investigations

- CBC, Hb, reticulocyte count
- RBC morphology
- ABC and Rh grouping of mother and baby
- Coomb's test of mother and baby
- Serum bilirubin, both direct and indirect
- Blood culture if sepsis
- Serum albumin and other LFTs
- Ultrasonography of abdomen and liver scan
- TSH

Management of Jaundice in the Newborn

1. *Send cord blood* for serum bilirubin, haemoglobin, direct Coomb's test, and blood grouping of child and mother when incompatibility is suspected. Bilirubin monitoring every 8–12 hours.
2. *Start phototherapy* when serum bilirubin is higher than 10 mg% or is rising fast (> 0.5 mg/hour). Bilirubin absorbs light maximally in blue range (420–470 nm), converts toxic bilirubin by photoisomerisation into unconjugated nontoxic isomers like lumirubin excreted in bile and urine. Eyes should be kept padded. Complications include loose stools, rashes, exposure hypothermia, and dehydration. Phototherapy to babies with direct jaundice causes the "bronze baby syndrome".
3. *Phenobarbitone* 5 mg/kg day orally to hasten maturation of the liver microsomal enzymes. Not useful after 7 days. Not a substitute for phototherapy. To be avoided as drowsiness due to phenobarb will intervene with correct assessment of onset of kernicterus.
4. *Tin (Sn)-Protoporphyrin* – administration has been tried. Bilirubin levels decline but there is no advantage over phototherapy. It inhibits conversion of biliverdin to bilirubin by haeme oxygenase.

5. *Exchange transfusion* if bilirubin level > 20 mg/100 mL in full term babies, and if > 18 mg/100 mL in prematures. It may be carried out at lower levels in premature babies, or if bilirubin level is rising rapidly in presence of evidence of haemolysis, sepsis, asphyxia or acidosis. Rough rule: Exchange level bilirubin = Wt. in gms/100. In Rh disease with Coomb's test positive, cord bilirubin > 5 mg%, cord Hb < 12 gm% are indications for exchange at birth. Exchange done with 160–180 mL/kg of semi-packed cells through catheter in umbilical vein.

Management of Pathological Jaundice

Phototherapy

Mode of action

- Structural isomerization converting bilirubin to lumirubin, which can be excreted into the bile without need for hepatic conjugation.
- Geometric photoisomerisation of unconjugated bilirubin with formation of more soluble form of bilirubin.
- Photo-oxidation – Bilirubin gets oxidised to colourless byproducts which are excreted in urine, the least important mechanism.

Indications

- Serum bilirubin >15 mg% for term infants and 10 mg% for preterm infants or 5 mg or more in first 24 hours.
- Hemolytic disease of newborn, seen after birth (in conjunction with exchange transfusion).
- Prophylactic therapy in extremely low birth weight or severely bruised babies.

Technique

- Light source – 4 blue fluorescent lamps and 4 daylight lights (effective radiance of 11 μm/cm^2/nm)
- Protection of infant – Eye patches to prevent adverse effects on retina
- Position – Baby lies naked with only diapers on at a distance of about 45 cm from light source.
- Duration – 24–48 hours exposure

Complications

- Increase in body temperature
- Dehydration due to insensible water loss
- Photosensitization resulting in skin rash
- damage
- Bronze baby syndrome – Skin, urine and serum brownish black after several days of phototherapy. Seen more often in neonates with conjugated hyperbilirubinemia. Full recovery after discontinuation of therapy
- Congenital erythropoietic porphyria – A rare condition with features of haemolysis, splenomegaly and pink urine, and bullous dermal lesions. Contraindication for phototherapy
- Diarrhoea due to high content of photodegradation products in gut

Exchange transfusion – is the standard immediate therapy for severe hyperbilirubinemia to prevent kernicterus and to correct anemia in erythroblastosis foetalis.

Indications

- Serum bilirubin > 20 mg/100 mL in full term babies and > 18 mg/100 mL in prematures
- Serum bilirubin rising by 1 mg/100 mL per day
- Severe anemia – Hb < 8 gm%

  Exchange at lower levels if sepsis, asphyxia or acidosis, Rh disease with Coomb's test positive, cord bilirubin > 5 mg%, cord, Hb < 11 gm%
- To prevent or improve cardiac failure in hydropic infants.

Type of blood – Blood withdrawn < 72 hrs preferred. In emergency, frozen RBCs reconstituted in saline or plasma can be used. ABO compatible Rh negative blood for erythroblastosis foetalis and O group Rh compatible blood for ABO incompatibility.

Quantity – Rough rule: exchange level: bilirubin wt. in gms/100. 160 ml/kg is used for one exchange transfusion.

Technique – Push and pull method in umbilical vein with a syringe and 4-way stopcock with aliquots of 5–10 mL at each push.

Complications

- Bacterial sepsis
- Bleeding – Thrombocytopenia, deficient clotting factors
- Vascular – Portal vein thrombosis, umbilical or portal vein perforation
- Cardiac – Arrhythmia, cardiac arrest, circulatory overload
- Electrolyte and metabolic – Hypocalcemia, hypoglycemia, hypomagnesemia, acidosis

Pharmacotherapy

Phenobarbitone – reduces serum bilirubin by more than 50% in physiological jaundice, but is effective only if given to the mother before delivery. Dose of 5 mg/kg/day. Hastens maturation of liver microsomal enzymes. Not a substitute for phototherapy.

Tin (Tn) and Zinc (Zn) porphyrins cause decline in bilirubin levels by inhibiting activity of haemoxygenase. Not a substitute for phototherapy.

Others – (a) *Frequent milk feeding* prevents reabsorption of unconjugated bilirubin from the gut reducing enterohepatic circulation. (b) *Agar* – Bilirubin-binding

agent in the gut 125 mg 3 hrly has the same effect. (c) *Albumin infusion* 1 mg/kg of salt-free albumin as an alternative to exchange transfusion in very small babies.

Hemorrhagic Disease of the Newborn

Types of neonatal haemorrhage:

1. *Haemorrhagic disease of the newborn* due to: (i) Low prothrombin level at birth due to deficiency of vitamin K. (ii) Fall of prothrombin on fourth or fifth day after birth. If it falls as low as 15–20% of normal, spontaneous haemorrhages are likely to occur. (iii) Immaturity of liver for formation of vitamin K-dependent factors. (iv) Relatively low concentration of vitamin K in breast milk. (v) Poor endogenous intestinal production until full colonization with intestinal bacteria. Common from day 2 to day 5 of life.
2. *Birth injuries,* e.g. superficial injuries of scalp, intracranial and visceral haemorrhages.
3. *Due to asphyxia or infection* in premature infants leading to DIC.
4. *Secondary to general or local* disease, e.g. syphilis, neonatal infections and septicaemia.
5. *Umbilical bleeding* due to mechanical cause, or after separation of the cord from an umbilical polypus, clotting factor deficiencies (especially factor xiii).
6. *Thrombocytopenia* due to trapping of platelets in big hematomas, intrauterine and neonatal infections, isoimmune.
7. *Rare blood disease*, e.g. haemophilia.
8. *Vaginal haemorrhage*, usually a manifestation of maternal hormone withdrawal, occurs on 5th–7th day, of no consequence.
9. *Swallowed maternal blood*.
10. *Mother on treatment* with coumarin derivatives, dilantin or phenobarbitone.

Symptoms and signs:

- *GI tract* – Haematemesis and melena are the most common manifestations. Sudden onset with passage of dark tarry stool on first or second day after birth. Stools that follow may consist of almost pure blood. Haematemesis occurs in about half the cases and usually follows melena. Infant soon becomes pale and collapsed and may die in a few hours or after 2 to 3 days.
- *Vagina* – may be the only site of bleeding which is usually slight and continues for 2–3 days, withdrawal bleeding seen normally after fifth day.
- *Haematuria* – usually slight loss of blood.
- *Umbilicus* — severe and even fatal bleeding may occur. It often starts in the form of a steady oozing at the end of the first week.
- *Lungs* – Acute haemorrhagic pneumonia may start within a few hours. Rapid pallor and blood stained froth in mouth. Rapidly fatal.
- *Intracranial* – if large, infant is stillborn; if less severe – asphyxia, inability to suck well and to swallow, poor ineffective cry, twitchings or convulsions, intermittent cyanosis, bulging fontanelle, rigidity of limbs. Squint, nystagmus and local paralysis may be present.
- *Adrenal* – may accompany other manifestations of anoxia at birth or later occur rarely as a part of clinical manifestation of haemorrhagic disease.
- *Skin* – Ecchymotic areas at points of pressure.
- *Miscellaneous* – Nose, mouth, conjunctiva and retina.

Management

1. Vitamin K_1 oxide – 1 mg/kg IV or Aqueous preparation of IM Menadione (vit-K_3) thrice, repeat at 8 hourly intervals.
2. Transfusions of fresh whole blood – 20 mL/kg if bleeding continues, or 10 mL/kg of fresh frozen plasma.

Prevention – Administration of vitamin K to the mother in the last months of pregnancy and during labour if mother on phenytoin or coumarin. Elective surgery like circumcision should be postponed till after a week, but if performed, vitamin K should be given parenterally. Vitamin K_1 mg to at risk neonates at birth, particularly prematures and low birth weight, forceps, LSCS and instrumental deliveries.

REGURGITATION AND VOMITING IN THE NEWBORN

Regurgitation is non-forceful expulsion of gastric contents from oesophagus or stomach through the mouth, unaccompanied by nausea or forceful abdominal contractions.

Causes

1. ***Physiologic*** – in early weeks, referred to as 'spitting up'. Of no concern if normal weight gain continues. Frequency lessens with age.
2. ***Faulty feeding techniques*** – Lack of burping, eructation of air when supine, prolonged feeding through small nipple, weak caloric formula, bottle-propping, all these lead to aerophagia.

3. ***Gastro-oesophageal reflux*** (Chalasia cardia) – Symptoms between 3rd and 10th day. Regurgitation when infant laid supine; prevented if held up for 30 minutes after feeding. Diagnosis by 24 hr. oesophageal pH monitoring with a pH probe.
4. ***Congenital oesophageal obstruction*** – Oesophageal atresia with or without tracheo-oesophageal fistula. Symptoms soon after birth – excess mucus at mouth, choking, cyanosis. Failure to pass No. 8 to 10 French soft rubber catheter into stomach confirms diagnosis.
5. ***Increased abdominal pressure at birth*** – Neonatal ascites, bilateral renal masses.

Vomiting – Causes

1. ***Mechanical causes***:

   Congenital anomalies of GI tract frequent in newborn – (a) Ileal, jejunal or duodenal atresia. (b) Imperforate anus. (c) Meconium ileus in first 24–36 hours early sign of cystic fibrosis. (d) Meconium plug – inspissation in distal colon. (e) Intestinal stenosis – duodenal, jejunal, ileal, rectal. (f) Malrotation. Duodenum obstructed in first 3 weeks. Midgut volvulus. (g) Pyloric stenosis – initially regurgitation of feeds in first week, vomiting in 2nd or 3rd week, constipation from birth, loss of weight. (h) Stomach torsion. (i) Diaphragmatic hernia. (j) Lactobezoar – obstruction from inspissated milk sugar. (k) Hirschprung's disease. (l) Paralytic ileus – Peritonitis, sepsis, hypokalaemia. (m) Gastric stasis common in proteus infection. Early sign of sepsis.

2. ***Reflex causes***:

   (a) *Stimuli from GI tract* – (i) Mucus or meconium gastritis – swallowing of amniotic fluid or meconium could be cause of unexplained vomiting in first 2–3 days. (ii) Gastritis from acute parenteral infection, severe respiratory infections, or bacterial gastroenteritis. (iii) Spontaneous gastric perforation (1st week). (iv) Peptic or duodenal ulcer. (v) Necrotizing enterocolitis of newborn. (vi) Haemorrhagic disease of newborn.

   (b) *Stimuli from urinary tract* – (i) Urinary tract infection in newborn. (ii) Uraemia.

   (c) *Inborn errors of metabolism* – Amino acid disturbances, organic acidaemias, galactosaemia.

3. ***Central causes*** – (a) Cerebral oedema – birth injury, asphyxia. (b) Intracranial haemorrhage. (c) Sepsis and neonatal meningitis.

Investigations:

A. History:

1. *Feeding history* – Time of onset of vomiting, history of frothing, choking, cyanosis, failure to gain weight, antenatal and intranatal events.
2. *Appearance of vomitus* – Gastric aspirate with bile more than 20 mL in newborn suggestive of intestinal obstruction. (i) Bilious – Definite sign of obstruction below ampulla of Vater. (ii) Non-bilious – Obstruction above ampulla. (iii) Uncurdled milk – Oesophageal atresia. (vi) Blood – Peptic or stress ulcer, sepsis, achalasia, haemorrhagic disease, swallowed maternal blood.
3. *History of polyhydramnios* – Oesophageal atresia, other GI obstructions. History of meconium-stained liquor in gastritis.
4. *Site and degree of abdominal distension* –Generalized if jejunal or ileal, epigastric if duodenal.
5. *Stool* – (i) Thick, tenacious meconium –meconium ileus. (ii) Malena – haemorrhagic disease, necrotizing enterocolitis, ulcers. (iii) Whitish stools – atresia distal to ampulla of Vater.

B. Examination:

1. *Abdominal examination* –pyloric lump, stomach peristalsis in hypertrophic pyloric stenosis, rubbery bowel loops in meconium ileus, scaphoid abdomen in diaphragmatic hernia, absent peristalsis in ileus. PR examination – imperforate anus, meconium plug.
2. *Chest examination* – Mediastinal shift to right with cyanosis suggests diaphragmatic hernia. Shift to the left rarely.

C. Investigations:

1. *Radiological features:*
   - Hyperperistalsis in early stages (on fluoroscopy).
   - String sign – A thin streak of barium extending between pyloric antrum and duodenal cap, representing the narrowed pyloric canal.
   - Beak sign – An abrupt cut-off of barium column in the pylorus, forming a very small curved point.
   - Shouldering – Indentation of barium-filled antrum as a result of hypertrophic pyloric muscle.
   - Single large bubble or double bubble in pyloric obstruction.
   - Tram track sign – A double track of barium may be observed, outlining hypertrophic mucosa, in the elongated pyloric canal.
   - Delay in gastric emptying.
2. *Ultrasonography.*
3. *Urine* – Routine, amino acids, culture.

4. *Blood CBC and culture.*
5. *For sepsis screen.*

Management

1. Stomach wash with sterile water or normal saline helps in mucus gastritis.
2. Small feeds of suitable concentration. Thickening of feeds with cereal in pyloric stenosis.

NECROTIZING ENTEROCOLITIS

Occurs in premature infants under stress in first week of life.

Pathogenesis

Mucosal injury – This is attributed to: (a) *Ischemic damage* to intestinal mucosal barrier, as a result of foetal distress, perinatal asphyxia, respiratory distress syndrome, hypothermia, congenital heart disease or following exchange transfusion for hyperbilirubinemia. (b) *Diarrhoea.* (c) *Bacterial infections* with E.coli, Klebsiella, pseudomonas. Also Clostridia, C. perfringens and C. butyricum. Stasis of intestinal contents favours bacterial overgrowth.

Milk formula feeding – Almost all babies are fed artificially prior to onset of illness. Poor systemic and gastrointestinal and mucosal protection against bacterial infections in preterm infants predisposes them to infection of the gut.

***Clinical features*:** These may be described in three stages:

Stage 1A: Suspected NEC – Unstable temperature, apnoea, bradycardia, lethargy, mild abdominal distension, vomiting.

Stage 1B: Blood in stools. X-ray shows mild intestinal distension.

Stage 2: Clinical features as in stage 1. Bowel sounds diminished. In more severe cases metabolic acidosis. Abdominal X-ray: *Pneumatosis intestinalis* and dilatation of intestines.

Stage 3: In addition to the above, infant has low BP, bradycardia, apnoea, acidosis, DIC and even anuria. There are signs of peritonitis with abdominal tenderness, erythema of abdominal wall and distension. X-ray may show portal vein gas (an ominous sign) and gas under the diaphragm if perforation has occurred.

Management

Stage 1: Conservative stop enteral feeds. Give IV fluids
Stage 2: Conservative + Antibiotic
Stage 3: Antibiotic + Surgery

3. CONGENITAL SYPHILIS

CLINICAL MANIFESTATIONS

1. *Constitutional symptoms* –
   Anaemia, wasting, fever, fretfulness.
2. *Marasmus* – Infant undersized, puny and marasmic with a wrinkled face and wizened appearance.
3. *Mucocutaneous lesions* –
   (a) Snuffles – due to rhinitis. It may be present at birth or appear after few weeks.
   (b) Laryngitis – causing the cry to be hoarse.
   (c) Skin rashes – (i) Maculopapular, circular, slightly elevated, and does not itch. The rash at first is bright red but gradually fades to a brownish colour. It may involve the entire body or be confined to the face, back and extremities. The rash and subsequent flaking on the soles and palms may give rise to a highly glazed appearance of the skin. (ii) Linear cracks or ulcers radiating from the mouth and anus. They are moist and produce fissuring and bleeding. Condylomata or raised greyish masses close to the anal margin or around the anus and female genitalia. (iii) Syphilitic pemphigus. (iv) Syphilitic onychia.
4. *Hair* – Eyebrows disappear, excess hair on head (syphilitic wig).
5. *Visceral* – (i) Liver usually enlarged, may extend to the umbilicus; firm, smooth and not tender. Jaundice indicates severe infection. (ii) Spleen – slightly enlarged. (iii) Kidneys – occasionally albumin, casts and blood cells in urine, rarely generalized oedema. (iv) Lungs – Pneumonia alba. (v) Orchitis.
6. *Ocular* – Iritis and choroiditis.
7. *Nervous system* – Meningitis.
8. *Bones* – (i) Osteochondritis – Swelling and tenderness at ends of long bones, and in severe cases separation of epiphysis. The condition is so painful that the infant may refuse to move the limb – "pseudoparalysis". (ii) Periostitis along the shafts of the bones. (iii) Dactylitis occasional. (iv) Skull bones – Craniotabes, Parrot's nodes, hydrocephalus.

DIAGNOSIS

X-rays of long bones – (a) Periostitis of shafts of long bones gives appearance of double margin or greatly thickened cortex. (b) Eroded areas (moth-eaten appearance) at upper end and inner aspect of tibia. (c) 'Cat-bite' deformity

of medial tibial condyle. (d) Widened and serrated epiphyseal lines, separation of epiphyses.

Serology – Treponemal tests positive in mother. Higher titre of baby compared to mother or rising titre after 3 months diagnostic in baby.

LATE CONGENITAL SYPHILIS

1. *Interstitial keratitis* – begins as a small pinkish grey patch near the margin of the cornea (salmon patch) which gradually spreads until the whole cornea is involved.
2. *Neurosyphilis* – Juvenile general paralysis more common than tabes, meningovascular syphilis, optic atrophy.
3. *Teeth* – (i) Hutchinson's teeth – the incisors of the second dentition are broader at the base than at the cutting edge in the centre of which there are notches. (ii) Moon's molars – molars dome-shaped.
4. *Bones* – Sclerosing osteitis and periostitis – sabre tibia, gummata of bones which might break down and leave a discharging sinus. Necrosis of nasal bones and hard palate not uncommon.
5. *Joints* – Painless effusion into the synovial cavities, most commonly the knees (Clutton's joints). Rarely multiple arthritis of smaller joints resembling rheumatoid arthritis.
6. *Visceral changes* – Liver may enlarge up to the umbilicus, surface may be irregular. Ascites and jaundice rare. Splenomegaly. Kidneys – albuminuria, casts and haematuria due to progressive renal fibrosis. Recurrent attacks of paroxysmal haemoglobinuria occur.
7. *Deafness.*

SYMPTOMS ACCORDING TO AGE

At birth... Pemphigus, progeric appearance, syphilitic wig, pneumonia, osteochondritis.

3–4 weeks... Skin eruptions, choroiditis, otitis, haemorrhage from umbilicus, nose or fissures.

3–4 months... Epiphysitis, fissures at lips and anus, condyloma, hepatomegaly and splenomegaly, gumma of testis.

6 months–1 year... Uveitis, bossing of skull.

1–2 years... Dactylitis, mental deficiency.

Late manifestations... Interstitial keratitis, deafness, periostitis of long bones, Clutton's joints, tertiary lesions of skin and mucous membrane, paroxysmal haemoglobinuria, neurosyphilis.

STIGMAS OR HALLMARKS OF PREVIOUS LESIONS OF CONGENITAL SYPHILIS

Mucocutaneous – Rhagades – peribuccal cicatrices radiating from mouth. Mucous membranes – saddle nose, perforation of palate.

Bones and joints – Bossing of head. Sabre shin.

Hutchinson's triad – (i) Eyes – keratic scar, chorioretinitis, pupillary changes, optic atrophy. (ii) Ear – deafness. (iii) Teeth – Hutchinson's teeth, mulberry molars.

Constitutional defects – Syphilitic facies. Dwarfism and infantilism. Mental deficiency.

Treatment: Benzathine penicillin IM daily for 14 days in dose of 50,000 U/kg eradicates CNS involvement.

4. GASTROESOPHAGEAL REFLUX DISEASE

It is now well established that transient lower esophageal sphincter relaxations (TLESRs) are the main mechanisms that underlie gastroesophageal reflux events.

Symptoms and Complications

Regurgitation, vomiting, persistent or sudden spells of crying for no obvious reason, choking, food refusal, anorexia, hiccups, failure to thrive.

Management

(a) Small, frequent feeds. Thickening of milk feeds (with rice cereal). (b) H_2 receptor antagonists, e.g. Ranitidine. (c) Proton pump inhibitors, e.g. Lansoprazole 0.2 mg/kg/day. (d) Prokinetic agents, e.g. Mosapride 0.1 mg/kg/day. (e) Surgery may be required in severe cases.

5. INFANT FEEDING

BIRTH TO 6 MONTHS

Breast milk: The ideal food for human infants is human milk, a complex band of nutrients and immunological and other bioactive substances that nourishes the baby, and helps to confer protection from bacterial and viral infections and assists in adaptation of life outside the womb (Table 17). It is the sole and sufficient source of nutrients from birth to about 6 months and its nutrient composition meets specific nutritional requirements of neonates; for example, the sodium, protein and fatty acid contents of human milk differ fundamentally from cows' milk which

Table 17: Principal advantages of breastfeeding

• Strengthens mother-infant bonding
• Natural and easier
• Helps uterine involution
• Partial contraceptive effect
• Confers protection to infants against infections
Immunoglobulin A
Lactoferrin
Lysozyme
Oligosaccharides
• Reduces risk to infant of GI disturbances
Obesity
Hypocalcemia
Hyponatremia
Hypothyroidism
Cow's milk protein intolerance
• Reduces risk of childhood and adult disease
Sudden infant death syndrome
Cardiovascular disease
Inflammatory bowel disease

Table 18: Antimicrobial factors in human milk

• Immunoglobulin A	Protects intestinal epithelium from luminal antigens
• Lactoferrin	Competes with bacteria for iron
• Lysozyme	Antibacterial enzyme lysis cell walls
• Oligosaccharides	Stimulate growth of lactobacilli in colon
• Macrophages	Engulf bacteria
• Lymphocytes	Secrete immunoglobulins (B) and lymphokines (T)
• Protease inhibitors	Inhibit digestion of bioactive proteins in milk
• Complement	Assists in bacterial lysis
• Interferon	Antiviral agent
• B_{12} binding	Compete with bacteria for folate-binding these vitamins proteins
• Antistaphylococcus factor	Lipid with antistaphylococcal action

is the basis of most bottled milk formulae. The composition of human milk changes during lactation and during a single feed. At the beginning of each feed, the fat content is low, but increases gradually such that most energy-dense milk is secreted at the end of the feed.

Colostrum is secreted by the breast during the first few days of lactation; it contains more protein (about 100 g/litre) than milk produced later (about 10 g/litre). Most of this protein comprises 'protective proteins', which help to defend the infant from GI and respiratory infections (Table 18).

The incidence of GI and respiratory infections is lower in breastfed babies than those receiving formula milk, because there are many protective factors.

'Demand' feeding requires that the mother watch for early feeding cues from the baby, such as rapid eye movements, lip-smacking, rooting or sucking on hands. The mother should put the baby to the breast when she observes these cues, rather than waiting for the infant to cry.

Infrequently allergens to which the infant is sensitised may be conveyed in the milk.

Contraindications:

a. Temporary – Fissuring or cracking of nipples, mastitis, acute illness in mother. Feeding should continue or expressed breast milk given.

b. Permanent – Infants with galactosaemia or congenital lactase deficiency, chronic poor nutrition, debility, epilepsy, severe neurosis or postpartum psychosis, severe diabetes, mother receiving drugs such as antithyroid drugs which are secreted in milk, deep breast abscesses. HIV and hepatitis B positive mothers can transmit infection to the baby in 20–25% cases.

6–12 MONTHS

Complimentary feeds should be offered after 4-6 months of age. May have to be given earlier if breast milk is not sufficient owing to poor advice on feeding and lack of stimulation. True lactation failure is very rare. Drugs like Chlorpromazine 25 mg t.d.s. or Metoclopramide 10 mg t.d.s. for 7 days are of limited value for enhancing lactation and cannot substitute for early initiation and frequent feeding. Weight gain, and urine output more than 6 times a day are most reliable indications of adequacy.

Expressed breast milk – can be obtained by hand or by pump. Used in sick infants or preterm infants and fed by cup, spoon or tube. Can be preserved for 6 hrs. at room temperature and 24 hrs. in refrigerator at 4–8°C without contamination. Can be taught to working mothers.

Weaning – For developing countries breastfeeding encouraged up to 2 years. Usually advisable until infant is 6–9 months old. Initially one of the breastfeeds is replaced by artificial feeding. After several days, another breastfeed is replaced and so on until the baby is entirely weaned. The total time required depends on the maternal

Table 19: Nutritional comparison of milks

Milk (per 100 mL)	*Human*	*Cow*	*Buffalo*	*Double-toned*	*Toned (Buffalo)*
Protein	1.2	3.5	4	3	3
Fat	4	4	7	1.5	3.5
Carbohydrate (Lactose)	7	4	4	4	4
Calories	67	67	103	40	67

milk supply. Bottle discouraged at all times owing to infection. Protein-rich solids begun after 6 months.

Artificial Feeding

1. *Whole fresh milk* – buffalo, cow. Dilution – 1:1 up to 1 month. 2:1 up to 2 months, undiluted later. Composition – in g/100 mL is shown in Table 19.
2. *Skimmed milk* – Low fat content is preferable for fat intolerance.
3. *Toned milk* – can be used undiluted in first 4–5 months.
4. *Powdered milk:*
   a. Whole milk powder.
   b. Skim milk powder.
   c. Humanised milk powder.
5. *Modified milk powder* – largely used for infant feeding. Animal fat is substituted with vegetable fats, and fortified with iron and vitamins. Reconstituted by adding one level measure (provided with the powder) to 30 mL of water.
6. *Soyabean milk* – used when lactose intolerance is proved. 100 mL reconstituted – 60 cals/100 mL and 2.1 g protein.

Feeding principles – consist of demand feeding.

- The quantum should be judged by the infant's needs and weight gain. 2-hourly breastfeeding during day and 3-hourly at night is recommended for maximal let-down.
- The principle is one of supply and demand encouraged by free interaction of breast and baby without 'an eye on the clock'.
- No check on feeding duration. Allow for up to 20–25 minutes, important for the baby to get "hind-milk" which is 3-fold higher in fat and 1.5 times higher in protein compared to the fore-milk.
- Emptying the breast encourages re-filling.
- Plain water should be avoided as it decreases breast milk intake and poses a risk for infection.
- Complete natural demand feeding is desirable against any schedule.
- Feedingbottles must be avoided. Clean vessel and spoon preferable.
- Breastfeeding should be discontinued latest by 2 years of age.
- No vitamin supplements are necessary up to 6 months in term infants of healthy mothers.
- Breast milk is a poor source of vitamin D containing 20–60 IU per litre which is not enough to protect against rickets. Hence, vitamin D supplement is necessary in exclusively breastfed babies.

In top feeding, the milk is warmed to body temperature. The sterile nipple should be applied without contaminating it. The hole of the nipple should be such that milk will drop slowly. The eructation of air (burping) swallowed during feeding is important for avoidance of abdominal discomfort and of regurgitation. Eructation is facilitated by holding the infant upright over the shoulder with or without gently patting the back. Making the child lie on the abdomen or on the right side also facilitates burping. A feeding may require 5–25 minutes depending on the vigour and age of the infant. In no instance should the baby be urged to take more than it desires.

Change over to solids – Green banana and cereal, mashed vegetable, dal, all introduced one at a time after 4–6 months. Eggs, minced meat gradually after 9 months to one year. Every new item of diet should be offered in small quantity – 1/2–1 teaspoonful at the beginning. If the infant tolerates it well, it can be gradually increased. Not more than one item of diet should be introduced per week.

6. GROWTH AND DEVELOPMENT

It is a process by which the fertilized ovum attains adult size. Growth implies changes in the size or in the values given for certain measurements of maturity. Development encompasses other aspects of differentiation of form or function including emotional and social changes as a result of environmental interaction.

FACTORS AFFECTING GROWTH AND DEVELOPMENT

1. *Genetic* – A legacy of biologic potential influenced by environment.
2. *Hormonal* – Growth hormone and its peripheral action compounds (somatomedins), thyroxine, insulin, sex steroids.
3. *Growth factors* – Nerve growth factor, cartilage factor, fibroblast growth factor and others with undifferentiated action.

4. *Trauma* – Prenatal or postnatal including infection, chemical or physical trauma or immunologic.
5. *Nutritional failure* – Antenatal malnutrition leads to IUGR and low birth weight which influences growth potential throughout life. Postnatal PEM (protein energy malnutrition), iron deficiency, trace element deficiency, vitamin deficiency.
6. *Socio-economic factors* – Closely influence nutrition, infection, developmental stimulation.
7. *Emotional factors* – modify growth potential. Deprivation leads to "emotional deprivation syndrome" which can stunt physical and psychological development. Position of child in family, interaction of parents and child, child-rearing patterns influence growth.
8. *Culturopolitical factors* – may limit development potential by establishing conventional behaviour patterns and expectations and alter schedule for acquisitions of motor and intellectual skills.
9. *Intellectual stimulation and learning.*

GROWTH PARAMETERS

1. ***Height or length:***

Foetus	8 weeks	:	2.5 cm
	12 weeks	:	7.5 cm
	28 weeks	:	35 cm
	Birth	:	50 cm

1 year: adds on 1/2 of birth length 75 cm
2 years: adds on 1/2 of 1st year's growth 87–88 cm

Thereafter till adolescence growth spurt about 6–8 cm per year.
Weech's formula that can be used from 2–12 years.
Age (yr) × 6 + 77 cm.

2. ***Weight:*** Sensitive growth parameter, first to decrease in acute malnutrition.

Foetus	8 weeks	:	1 gm
	12 weeks	:	14 gm
	28 weeks	:	1000 gm

Birth: 2.5–3.7 kg. Less than 2.5 kg considered low birth weight. Weight loss in first 10 days up to 10% body weight. Thereafter, increase of 20 gm per day for first 5 months and about 15 gm per day up to 12 months. Baby doubles birth weight at 5 months, triples at 1 year.
2nd year: gains 2.5 kg
3–5 years: gains 2 kg per year
6–12 years: gains 2–2.5 kg per year.

Approximately 15 kg at 5 years, 25 kg at 10 years, 40 at 15 years.
Weech's formulae for average weight (in kg)

3–12 months	$\frac{\text{age (mths)} + 9}{2}$
1–6 years	age (yrs) × 2 + 8
6–12 years	$\frac{\text{age (yrs)} \times 7 - 5}{2}$

3. ***Skull circumference:*** A good measure of brain growth. Maximal in first year, reaches 90–95% adult size by 4 years. Birth: 32–35 cm (less than 30 cm microcephaly)
First 3 months: 2 cm per month (avg. 39 cm)
4–6 months: 1 cm per month (avg. 42 cm)
6–12 months: 1/2 cm per month (avg. 46–47 cm)
2nd year: 2 cm (48–49 cm)
3rd year: 2 cm (50–51 cm)
4th year: 2 cm (52–53 cm)
Adult: 53–56 cm

Up to 13 months use formula 1/2 × length (cm) + 10 cm ± 2.5 cm.

4. ***Surface area:*** It bears constant relation to nutritional factors affecting growth. Best calculated from normograms involving average weight and height.
Crude methods are:
$(m^2) = {}^3wt^2$ (kg) × 0.1
Simpler formula:
1.5 kg m^2 = (0.05 × kg) + 0.05
6–10 kg m^2 = (0.04 × kg) + 0.10
11–20 kg m^2 = (0.03 × kg) + 0.20
21–40 kg m^2 = (0.02 × kg) + 0.40

5. ***Upper to lower segment ratio:*** Upper segment measured from vertex to pubic symphysis. Important in assessment of growth disturbances – proportionate or disproportionate dwarfs. Ratio changes with age and height. Marginal difference between males and females.

Premature	> 1.7
Full-term newborn	1.69
1 year	1.54
2 years	1.44
3 years	1.33
4 years	1.27
5 years	1.21
6 years	1.14
7–12 years	1.10–0.98

Ratio retarded for age in hypothyroidism, achondroplasia and other short-limbed dwarfisms, rickets with lower limb deformities.

Table 20: Chronology of dentition

	Primary tooth eruption		*Permanent tooth eruption*	
	Maxillary	*Mandibular*	*Maxillary*	*Mandibular*
Central incisors	6–8 mths	5–7 mths	7–8 yrs	6–7 yrs
Lateral incisors	8–11 mths	7–10 mths	8–9 yrs	7–8 yrs
Canines	16–20 mths	16–20 mths	11–12 yrs	9–11 yrs
First premolars	–	–	10–11 yrs	10–12 yrs
Second premolars	–	–	10–12 yrs	10–13 yrs
First molars	10–16 mths	10–16 mths	6–7 yrs	6–7 yrs
Second molars	20–30 mths	20–30 mths	12–13 yrs	12–13 yrs
Third molars	–	–	17–25 yrs	

Table 21: Sexual maturity

	Boys	*Girls*
1. Adolescent growth spurt	13–15.5 years	11.5–14 years
2. Average increase in height	20 cm After 18 years 2.5 cms remain	8 cm After 18 years 1–2 cm remain
3. First sign of puberty	Increase in length and colour of pubic hair	Breast bud visible or palpable
4. Age at start of puberty	12–13 years	11–12 years
5. Duration of puberty to adult sex characteristics	4 years	2–2.5 years to menarche May be as long as 6 years

Ratio advanced for age in – Short trunk dwarfisms, acquired spinal diseases with kyphosis or scoliosis, e.g. tuberculosis, hypogonadism (Klinefelter's syndrome), Marfan's syndrome.

6. ***Chest circumference:*** Smaller than head circumference by 2–3 cm. Cross-over of head and chest circumferences takes place in Indian children at about 2 years of age (about 1 year in white races).
7. ***Mid-upper arm circumference:*** taken at midpoint of acromion and olecranon. Index of malnutrition constant at 1–5 years at 16–17 cms.

   Mild PEM 13.5–16 cm
   Moderate PEM 12.5–13.5 cm
   Severe PEM < 12.5 cm
8. ***Chronology of dentition:*** See Table 20.
9. ***Ossification centre appearances in infancy and childhood:***

   Birth: Distal femoral, proximal tibial, cuboid.

   3 wks: Head of humerus

   2–4 mths: Hamate, capitate

   4–6 mths: Head of femur

   1 year: Distal radial

   2 years: Distal tibia and fibula, capitulum of humerus.

   3 years: Triquetral bone, heads of metacarpals and phalanges of hand.

   4 years: Lunate, navicular of foot, greater trochanter of femur.

   5–6 years: Scaphoid, trapezoid, trapezium, lower ulnar epiphysis, upper epiphysis of radius, medial epicondyle of humerus.

   7–8 years: Lower epiphysis of ulna.

   9–10 years: Olecranon, trochlea of humerus, pisiform.

   11–12 years: Lateral epicondyle of humerus.
10. ***Milestones of development:*** *Importance:* (a) Assessment of step by step age-wise physicomotor and mental development. (b) Early detection of motor disorders, cerebral palsy, mental retardation, speech, auditory and visual defects. (c) Assessment of aetiology of developmental delay – congenital if poor milestones development from beginning, acquired or hereditary/acquired degenerative neuromuscular or CNS disease if arrest occurs after certain stage is reached. (d) Assessment of approximate point in time when pathology began, e.g. age at which malnutrition set in to cause development retardation.

    Classification:
    - Motor.
    - Adaptive – (a) Fine motor. (b) Visual. (c) Auditory.
    - Social.
    - Language – (a) Perceptive. (b) Expressive.
11. ***Sexual maturity:*** See Table 21.

7. PREMATURITY AND LOW BIRTH WEIGHT

Babies born before 37 weeks of gestation are called preterm (PM). Those weighing less than 2500 gm (10th percentile for gestational age) are called low birth weight (LBW) babies. Low birth weight may be due to prematurity or intrauterine growth retardation. The latter group are called small for date (SFD). Premature babies may be small for date also.

CLINICAL FEATURES

1. Length is short (less than 46 cm) in preterm. It is relatively normal for weight in SFD babies.
2. Head appears large compared to the rest of the body, particularly in SFD babies.
3. Only one of the two transverse creases on sole of the foot up to 37–38 weeks.
4. Breast nodule absent up to 33–34 weeks.
5. Scalp hair tends to be short and fuzzy up to 37 weeks.
6. Ear cartilage is poorly developed and the folds of the helix and anti-helix do not stand out till 36 weeks.
7. Testes descends and the scrotal rugae develop after 36 weeks.
8. Sucking and synchronized deglutition develop after 33 weeks.
9. Moro's reflex develops after 32 weeks.
10. Pupillary reaction to light develops after 31 weeks.
11. Blink response to glabellar tap develops after 31 weeks.
12. Strong flexor response to extension of forearm develops after 35 weeks.

COMPLICATIONS

1. *Hypothermia* – because of poor subcutaneous fat insulation, increased surface area compared to weight, immature hypothalamus and lack of brown fat that can be readily burnt for energy.
2. *Infection* – Septicaemia, meningitis and sclerema neonatorum. Baby appears lethargic, becomes pale, hypo- or hyperthermic. Abdominal distension, vomiting and paralytic ileus may develop. Skin becomes thick and adherent to underlying tissue (sclerema neonatorum). Polymorph functions and complement factors are depressed in PM.
3. *Respiratory distress syndrome* – due to hyaline membrane disease in PM, pneumonia and meconium aspiration in SFD.
4. *Apnoeic spells* – due to prematurity, intracranial haemorrhage, intra-pulmonary haemorrhage, hypoglycemia, hypothermia, sepsis.
5. *Hypoglycemia* – Baby becomes lethargic, develops convulsions or cyanosis.
6. *Retinopathy of prematurity (ROP)* – Multifactorial. Primary cause is prematurity, hyperoxia is also important. More sick the child, greater the risk.
7. *Anemia* develops within 4 weeks in preterm, SFD have polycythemia.
8. *Hypocalcemia* more in SFD.
9. *Pathological jaundice* in PM due to liver immaturity.
10. *Intraventricular-periventricular haemorrhage* – More common in PM. Can be spontaneous in babies less than 34 weeks. Aggravated or precipitated by asphyxia. Severe grades die or survive with mental handicap and cerebral palsy. Incidence reduced by gentle handling and thus preventing surges in BP.
11. *Persistent ductus arteriosus* – Higher incidence in PM because of influence of PGE_2 keeping ductus open. Can cause cardiac failure.
12. *Necrotizing enterocolitis* – common in PM with sepsis.
13. *Osteopenia* and rickets may occur in very small preterms.
14. *Oedema* may occur without obvious cause or due to intrauterine pressures.
15. *Late metabolic acidosis* may develop during 2nd or 3rd week especially if fed artificial milks.
16. *Massive pulmonary hemorrhage* may develop with asphyxia, infection or hypothermia, more common in SFD.
17. *Persistent pulmonary hypertension of the newborn (PPHN)* – occurs due to failure of normal drop in pulmonary arterial pressure after birth. Seen in FT or preterm babies. Birth asphyxia and meconium aspiration are common causes.

MANAGEMENT

1. *Warm chain* – A set of interlinked procedures carried out at birth and subsequently – (a) Warm delivery room. (b) Warm resuscitation facilities. (c) Drying the newborn immediately after delivery followed by (d) Skin to skin contact between infant and mother or putting the infant in an incubator or using radiant warmers. (e) Breastfeeding. (f) No baby bath at birth (g) Appropriate clothing and bedding covering the head conserves 2/3 of body Heat. (h) Mother and baby are nursed together. (i) Maintaining rectal temperature at 37°–37.2° in preterm babies.
2. *Feeding* – Feed the infant with a nasogastric tube till good sucking develops. Aim at giving 120 to 150 calories and 120 to 150 mL of fluid per kg of body weight, by the 6th or 7th day of life. Add 20–30 mL/kg extra fluid if on radiant warmer or phototherapy. Feeds should be given in small equally divided quantities every 2–3 hours round the clock. Start feeding early by the 6th hour of life, unless respiratory distress develops. Tube feeding with No. 5 or 6 infant tube if gestational age less than 34 weeks. Sucking

Table 22: Classification of milestones

Age	*Motor*	*Adaptive*	*Language*	*Social*
Neonatal period (4 weeks)	Prone: Flexed attitude, buttocks high. Supine: Flexed Moro active, grasp, stepping, placing reflexes.	Fixates face in line of vision. Startles with sound.	Cry	Visual preference for human face.
4 weeks	Prone: Legs more extended, buttocks down. Head lift momentary to body plane. Supine: More extended, tonic neck attitude.	Watches person, follows object 45° on one side.	Cry more meaningful, distinguishable hunger, pain	Body movements with social contact. Social smile.
8 weeks	Prone: Extended attitude. Raises head and sustains in line of body. Supine: Tonic neck posture. Head lags, less in traction position.	Follows object 45° on either side of midline.	Coos in response	Smiles on contact
12 weeks	Prone: Lifts head, arms extended, head above body plane. Supine: Tonic neck posture. Moro's, involuntary grasp, walking and placing reflexes go. Early head control with bobbing motion.	Reaches out for object and misses. Slight palm opening. Follows light 180°.	Makes 'aa' vowel sounds. Listens intently to voice. Cannot localise sound.	Sustained social Contact
16 weeks	Lifts head and chest, legs extended, arms outstretched. Symmetrical posture now, head in midline.	Hands in midline, tries to grasp with both hands and misses object. Follows ball rolling on table.	Turns head to sound. Laughs out aloud.	Displeasure if social contact broken, excited at sight of food.
20 weeks	Turns over prone to supine. Lifts up head, half of chest, arms outstretched. Sits with support with rounded back.	Goes out for object with one hand, may miss. Grasps voluntarily if object placed in hand.	Vowel sounds. Pitch variations.	Plays with strangers, demands prolonged contact.
24 weeks	Turns over supine to prone. Sits propped up with straight back momentarily without support. Supports weight on legs.	Grasps object offered, waves it in hand. Attempts to mouth it. Binocular vision develops. Regards mirror image.	Grunts, growls. Says 'ga-ga'.	Responds to name. Initiates contact by making sounds. Knows strangers.
28 weeks	Pivots: squirming movements. Sits on his own with hand support. Bounces when stood up.	Grasps large object with intermediate palmar grip, transfers objects, mouths actively, rakes at small objects.	Polysyllabic vowels. Bubbles at mother.	Enjoys mirror. Pits image. Cries if shouted at.
36 weeks	Sits up alone and well with support with a straight back. Creeps on all fours.	Radial grasp of objects. Assisted pincer grasp. Rakes at small object with index finger.	Monosyllabic consonants – labials 'ma', 'ba'. Can announce his arrival with sounds. Understands 'No'.	Develops fear of strangers. Plays 'peek-a-boo'.
40 weeks	Pulls to standing position. Stands with support. Crawls on fours.	Pincer grasp. Uncovers hidden toy. Retrieves dropped object. Releases objects grasped by others. Looks at picture.	Repetitive Consonants 'mama', 'baba'.	Waves 'bye bye'.
1 year	Walks with one hand held or cruises along furniture.	Unassisted pincer grasp for small objects; releases object on request or gesture.	4 to 5 words. May try to imitate spoken word. Understands commands.	Plays simple ball game. Simple postural adjustments to dressing.

Contd...

Contd...

15 months	Walks alone. Crawls upstairs but cannot come down.	Inserts pellet in bottle. Makes a line with pencil held like dagger. Tower of 2 cubes. Scribbles.	Jargon. Follows simple commands. May name familiar object.	Gives up bottle. Shows needs by pointing.
18 months	Runs stiffly. Walks upstairs one hand held, both feet on step. Explores places. Climbs on chair. Gait broad-based.	Imitates vertical stroke. Dumps pellet from bottle. Tower of 3 cubes.	Vocalises needs 10 words average. Names pictures. Obeys 2 serial commands.	Feeds self. Bowel control.
2 years	Runs well. Walks up stairs alternate feet. Downstairs one step at a time. Opens doors.	Tries to draw circle. Tower of 6 cubes. Folds paper once.	Puts 3 words in a sentence. Relates experiences. Names animals. 200–300 words.	Sphincter control by day. Helps undressing.
2½ years	Climbs down stairs. Kicks. Jumps.	Horizontal and vertical strokes, cannot cross them, closes circular figure. Tower of 18 cubes.	Uses pronoun 'T'. Knows full name. Physiological stammer.	Imitates others. "Parallel play".
3 years	Stands on one foot. Rides tricycle.	Copies circle, forms a cross. Tower of 9 cubes. Forms 'bridge' of 3 cubes.	Knows age and sex. Counts 3 objects well. Full sentences. Uses plurals and prepositions.	Dry by night. Plays with other children.
4 years	Hops. Climbs well. Throws ball over-hand.	Uses scissors. Draws a man with 2 to 3 parts Copies square. Hand dominance.	Tells stories 1600 words, 4 words per sentence. Knows colours.	Social interaction and role-playing. Runs errands.
5 years	Skips.	Names heavier of 2 weights. Copies triangle. Draws man with 3–4 parts.	Sentence of 5 words, counts 10 objects well.	Asks questions about meanings.
6 years	Acquires finer motor skills. Simple gymnastics.	Draws full man with clothes. Adds and subtracts.	2600 words.	Knows time of day. Knows right from left, good from bad.
7 years	—	Copies a diamond.	Most childhood difficulties gone. Speech clear.	Avoids self-exposure. Knows about sex.

and swallowing coordination develops after 34 weeks, when direct cup or spoon feeding of expressed breast milk can be started. Breast milk from the PM infant's mother is preferred as the preterm mother's milk is higher in protein and immunoglobulin with higher sodium content than term infant's mother's milk. Strict barrier nursing observing aseptic technique is imperative, because of proneness to infection.

3. *Vitamins* – Give 1mg of vitamin K IM at birth. Start vitamin C and multi-vitamin drops by 10th day of life. Vitamin E has a role in preventing specific haemolytic anemia. No iron for 4–6 weeks.

Apnoea of prematurity is treated with IV Aminophylline 5 mg/kg bolus followed by 1–2 mg/kg 8–12 hrly. The drug Doxapram is equal in efficacy. CAPP beneficial

Meconium aspiration can be fatal in SFD. Watch for 24 hrs for development of respiratory distress. Add antibiotics only if X-ray chest shows haziness or bilateral emphysema. Meconium is sterile but is a good medium for secondary infection. Ventilatory care.

8. FAILURE TO THRIVE

Failure to gain and often loss of weight in infants (and children) in absence of apparent cause (Table 23).

CLINICAL PICTURE

1. Failure to gain weight.
2. Failure to grow at expected rate.
3. Signs of developmental retardation.
4. Signs of physical and emotional deprivation – apathy, listlessness, lack of interest in surroundings, poor hygiene, withdrawal, intense eye contact with others.
5. Disorders of appetite – Anorexia, voracious appetite, pica.

Table 23: Causes failure to thrive

I. Inadequate intake –
Environmental causes
• Inadequate food intake due to ignorance and poverty.
• Emotional deprivation including maternal deprivation.
• Environmental disruptions.
• Rumination (controlled regurgitation of feeds).
• Child abuse, withholding of food.
• Psychiatric causes – infantile autism, childhood schizophrenia, anorexia nervosa in adolescence.
Organic causes
• Inability to suck due to prematurity, birth trauma, congenital malformations such as cleft palate and upper GI obstructions, cerebral palsy.
• Chronic vomiting.
II. Lack of digestion –
1. Chronic iron deficiency anemia.
2. Lack of bile in biliary atresia.
3. Pancreatic insufficiency in cystic fibrosis.
4. Chronic active hepatitis.
III. Impaired absorption –
1. Chronic diarrhoea.
2. Chronic infestation, e.g. giardia.
3. Intestinal malabsorption syndromes –congenital disaccharide deficiency, cystic fibrosis, coeliac disease.
4. Structural intestinal defects.
IV. Impaired utilization –
1. Chronic infections – Tuberculosis.
2. Respiratory – Asthma, cystic fibrosis, bronchiectasis
3. Endocrine disorders – Hypothyroidism, hyperthyroidism, hypoadrenalism, growth hormone deficiency, diabetes insipidus.
4. Chronic kidney failure.
5. Congenital heart disease, especially cyanotic.
6. Malignancy.
7. Chronic haemolytic anemia, e.g. thalassemia.
8. Inborn errors of amino acid and carbohydrate metabolism.
9. Collagen diseases.
10. Occult malignancy.
V. Hereditary –
1. Chromosomal disorders – Down's syndrome. Turner syndrome.
2. Primordial dwarfism.
3. Syndromes with premature ageing – progeria.
4. Cerebral malformation, cerebral degeneration.

6. Others depending on aetiology – Fever, polyuria, pallor, chronic constipation, vomiting, diarrhoea, dehydration, bulky foul stools (steatorrhoea), central cyanosis, acidosis, open anterior fontanelle, CNS signs of mental retardation or cerebral palsy, stigmata of chromosomal anomalies.

DIAGNOSIS

1. *History* – especially for environmental causes.
2. *Growth chart* – Identifies point of failure to thrive, may uncover causes, shows response to treatment. Aids diagnosis of constitutional short stature and hypopituitarism.
3. *Physical examination* – points to organ systems, CNS defect, cleft palate. Developmental and psychiatric evaluation.
4. *Investigations:*
   - CBC for infection, anemia.
   - Urine – routine, pH, sp. gravity, culture.
   - Stool – Ova and parasites. Tests for malabsorption – fat globules, 72 hours fat excretion, stool trypsin, stool pH and reducing substances for carbohydrate malabsorption.
   - Biochemistry – BUN, creatinine, electrolytes, sugar, LFT.
   - Radiograph – Chest, abdomen, sonography
   - Mantoux test.
   - Others – Chromosomal analysis, haemoglobin electrophoresis, sweat chlorides, tests of endocrine function.

PROGNOSIS: Non-organic ones eventually attain normalcy. Over half remain emotionally disturbed, have school problems. Small number die suspiciously. In case of organic cause prognosis depends on underlying disease.

MANAGEMENT AND PREVENTION

1. *Temporary change of environment* – Hospitalization may ease tension and cause dramatic improvement in weight gain and social interactions.
2. *Treatment of organic disease.*
3. *Parental education,* birth spacing, family planning, marital counselling.
4. *Early recognition* of *'at risk' families* – Immature parents, drug addiction, anti-social behaviour, child dislike, economic and emotional instability, single parent, family tragedy.

5. *Support* – From physician, social worker, family welfare agency, temporary foster care.

9. MALNUTRITION IN INFANTS AND CHILDREN

Malnutrition is the cellular imbalance between supply of nutrition and energy and the body's demand for both of them to ensure normal growth, maintenance and specific tissue functions.

Kwashiorkor and *Marasmus* are classical syndromes of childhood malnutrition. Although their clinical features appear to be distinct, many children have features of both. However, oedema is the only characteristic, other than weight deficit, that must be present for diagnosis of kwashiorkor. Marasmus is simply severe cachexia with weight loss as a result of wasting in infancy or childhood. The cut off point for the severity of wt. loss is 60% of expected wt. for age. Severity of wt. deficit and presence of oedema are the criteria for the Wellcome classification of severe malnutrition in children is given in Table 24. Table 25 gives age-dependant classification of Protein Energy Malnutrition (PEM).

KWASHIORKOR

Literally means 'the neglected one' and describes the young infant (usually from months to 2 years) displaced from the mother's breast by the succeeding infant.

Aetiology and Pathogenesis

- Kwashiorkor develops in those on diets with a low protein: energy ratio. Protein may be a limiting factor on such diets but the view has been challenged. Free radical-induced and possibly other damage to tissues caused by deficiencies of essential nutrients and coexisting infections may be an important reason why some children develop oedema and skin lesions.
- The initial endocrine responses in kwashiorkor are high insulin and low plasma cortisol levels, which promote uptake of amino acids by muscle, diverting them from the liver. As a consequence, there is reduced synthesis of albumin (resulting in hypoalbuminemia, which causes oedema) and apoproteins which predispose to fatty liver.
- These children have multiple infections, including tuberculosis and gastroenteritis. Infection may divert amino acids for synthesis of acute- phase proteins, thereby further reducing albumin synthesis. Fatty liver may develop.

Dysadaptation therapy – Suggests that children with marasmus are adapted to the deficient protein intake. In such children there was loss of fat and degradation of muscle protein secondary to hormonal responses, i.e. high cortisol and low insulin levels. The protein thus derived was used for generation of proteins including albumin, hence the absence of oedema and hypoalbuminemia. In Kwashiorkor, this adaptation does not occur.

Clinical Features

(a) Anorexia, diarrhoea, anemia (mainly iron deficient), irritability (leave me alone attitude) or apathy. (b) Dystrophic changes in skin and hair – skin becomes dry, thin, shiny or wrinkled (xerosis). The peeling plaques of dermatosis are labelled 'crazy paving' or 'flaky paint' dermatoses. The hair is thin and easily pulled out. During better periods of nutrition, scalp hair may grow normally, but a fresh band of abnormal hair would appear during another period of malnutrition (flag sign). Skin and hair changes are variable and may be accompanied by hypopigmentation. Depigmented hair is possibly mediated by zinc deficiency.

MARASMUS

When dietary energy is limited through chronic inadequate food intake, low insulin and high plasma cortisol levels result in release of amino acids from liver and their subsequent availability for hepatic synthesis protein (particularly albumin). The result is severe muscle wasting with normal plasma albumin levels and, hence no oedema. Absence of oedema in presence of severe muscle wasting in an infant or 1 year old child is characteristic of marasmus. Table 26 gives differentiating features of kwashiorkor and marasmus.

Table 24: Wellcome classification

Wt. for age	*Oedema*	
(% of expected)	Present	Absent
50–60	Kwashiorkor	Undernutrition
<60	Marasmic Kwashiorkor	Marasmus

Table 25: Age-dependant classification of protein energy malnutrition (PEM)

Nutritional status	*% Wt. for age*
Normal	> 80
1st degree	70–80
2nd degree	60–70
3rd degree	50–60
4th degree	< 50

Table 26: Differentiating features of Kwashiorkor and Marasmus

Kwashiorkor	*Marasmus*
Little wasting	Severe wasting
Oedema	No oedema
Subcutaneous fat present	Subcutaneous fat minimal
Serum albumin low	Serum albumin near normal
Enlarged fatty liver	
High prevalence of infection	

Marasmic kwashiorkor. Sometimes an infant or young child presents with features of both marasmus and kwashiorkor (oedema with severe muscle wasting).

Kwashiorkor equivalent – A well-nourished infant is suddenly switched off from all proteins including milk and instead fed carbohydrate rich foods (sugar baby). Since the energy needs are sufficient, the fat is not mobilized but, the protein deficiency results in hypoalbuminemia and oedema. The infant looks plump and pale (due to good subcutaneous fat).

Stunting – Persistent suboptimal food intake associated with recurrent and episodic malnutrition in children can result in short stature. Such children fail to achieve their maximum growth potential for growth, despite 'catch-up' growth during intervening periods of nutritional repletion or when free from infection.

Obesity – It is also a type of malnutrition. WHO has recommended the use of Body Mass Index (BMI = weight in kg/height in m^2) as an indicator of obesity. If BMI is in excess of 95th percentile for age and gender between 85th and 95th percentile, it is considered "overweight".

Management of Severe Malnutrition

Immediate treatment includes resuscitation – Correction of fluid and electrolyte disturbances, such as acidosis, hypoglycemia and hypothermia, and treatment of localized or generalized infections (e.g. bronchopneumonia, septicaemia). In kwashiorkor, an acute diarrhoeal illness often compounds. Chronic infections, such as tuberculosis, and chest infections are common.

Principles of management – Two-stage process: stabilization (usually for up to 7 days) followed by rehabilitation.

Stabilization – Correction of hypoglycemia, dehydration (glucose 25% IV 4 mL/kg bolus) and fluid and electrolyte imbalances (e.g. potassium chloride 4–5mEq/kg/day).

Hypothermia dealt with wrapping blankets, radiant warmers to maintain rectal temperature at 37°C. Because malnourished children do not exhibit the classical signs of infection (fever and leucocytosis), routine administration of antibiotics is advisable to control infection.

Refeeding must be initiated gradually. Overfeeding may also provoke acute liver failure. A suitable regimen provides 80 kcal/kg body wt./day and 0.7 g protein/kg body wt/day. Feeds small, every 2–2½ hours by tube if needed. Milk with 2 teaspoons of sugar/100 mL milk forms basis of feeding unless lactose intolerance is documented (stool pH < 6 and Benedict's test on stool > 2+ positive reaction). Banana, rice and dal, vegetable oil for calories. Egg as a flip with milk and water is a good source of first class protein. Dal, rice and buttermilk can be given if lactose intolerance. Micronutrients may be needed in amounts greater than normal daily requirement, to replenish stores and avoid further depletion related to tissue growth. For example as wasted muscle regrows, there are specific needs for potassium, iron, zinc and phosphate to avoid deficiencies (refeeding syndrome). Hypoalbuminemia is not helped by use of a high-protein diet, which can impair renal function.

Nutritional rehabilitation follows when the oedema has resolved and the child has recovered clinically, has a good appetite and begins to gain weight. This may take several weeks.

10. DEFICIENCY DISEASES

RICKETS

Aetiology

Age – From 4 months to 2 years, also in prematures. *Diet* – Less common in breastfed infants, may develop if mother's diet is poor. *Growth* – Rickets will only develop if growth is taking place, marasmic infants are seldom rachitic, but as soon as the infant begins to put on weight rickets is likely to develop. Dark-skinned infants more prone, lack of adequate exposure to sunlight.

Classification of Rickets

- ***Dietary deficiency of vitamin D*** (inadequate intake of calcium, vitamin D exposure to sunlight).
- ***Secondary rickets:*** due to malabsorption, e.g. coeliac disease.
- *Resistant rickets:* Resistance to therapeutic doses of vitamin D, e.g. familial hypophosphatemia rickets or Vitamin D dependent rickets.
- *Renal rickets* (Poor conversion of 25 OH-D_3 to 1.25-dihydroxy D_3 – active principle of vitamin D_3) in chronic kidney failure.
- *Malignancy* – Tumour-based rickets.

- *Hereditary forms* – (i) Vitamin D-dependent rickets (VDDR) – deficiency of 1-hydroxylase enzyme, autosomal recessive, low calcium type. (ii) Vitamin D Resistant Rickets (VDRR) – Primary defect is phosphorus wasting by proximal tubule (low phosphorus type). Also called type II rickets due to end organ defect. Inherited as X-linked dominant, autosomal director. Elevated levels of circulating calcitriol.

Clinical Features

1. *Head* – apparently larger than normal in horizontal diameters, forehead prominent (frontal bosses) and occiput and vault flattened out, hot-cross bun appearance, anterior fontanelle larger than normal and closing delayed, posterior portion of the skull in the first year may have demonstrable softening on pressure (ping-pong resilience, craniotabes). Frequent rocking movements of the head common, face appears small upper jaw being narrow, temporary teeth usually appear late. Excessive sweating over forehead.
2. *Thorax* – Beading of ribs at the junction of ribs with costal cartilages, best developed in the 4th, 5th and 6th ribs just external to the nipple – rachitic rosary. Sternum unduly prominent producing a "pigeon breast". Horizontal depression corresponding to insertion of the diaphragm below which there is a flaring of the ribs (Harrison's groove), occasionally funnel shaped depression of lower part of sternum.
3. *Spinal column* – Kyphosis due to weakness of muscles, which disappears if child is suspended from armpits. In severe cases after weight bearing scoliosis.
4. *Extremities* – Metaphyseal enlargement at wrists and ankles; knock-knee and bow legs; coxa vara, curving of bones of forearm outwards. Upper to lower segment ratio retarded for age, dwarfism in severe cases. Multiple greenstick fractures in severe rickets. Deformities may occur due to malunion. "Double-malleolus" at ankle.
5. *Ligaments and muscles* – relaxed and weak, hence deformity of spine, late standing and walking and over extension of knee joints – "acrobatic rickets".
6. *Digestive system* – Pot-belly due to weakness of abdominal muscles, and ptosis of liver and spleen.
7. *Nervous symptoms* – Restlessness at night with rocking of head on the pillow. Predisposition to tetanic convulsions.
8. *Respiratory system* – Adenoid and tonsillar hypertrophy, rhinitis, pharyngitis, bronchitis and bronchopneumonia common. In severe cases, tachypnoea with largely diaphragmatic breathing.
9. *Spasmophilia* – Triad of tetany, laryngismus stridulus, and convulsions may be expected in the low calcium type of rickets. High pitched distressing cry.

Diagnosis

Early signs of rickets – (a) Restlessness and irritability. (b) Sweating of head. (c) Head rolling. (d) Craniotabes. (e) Beading of ribs. (f) Anterior fontanelle noticeably big. (g) Enlargement of metaphyses at the wrists. (h) Delay in dentition.

Radiology

- Loss of zone of provisional calcification and widened growth plate
- Fraying of metaphysis – metaphyseal margins tend to be blurred and indistinct
- Splaying (widening of the metaphysis) and cortical spurs
- Cupping of the metaphysis
- Rachitic rosary
- Bowing of tibia (in long standing cases)

Laboratory

(i) Increased alkaline phosphatase in plasma earliest change. (ii) Low concentration of phosphorus except in late renal osteodystrophy where it may be high. (iii) Calcium level may also fall in tetany though it is usually normal, low in VDDR, can fall with infections, high phosphorus diet, alkali administration, administration of low doses of vitamin D. (iv) Generalized aminoaciduria except in VDDR.

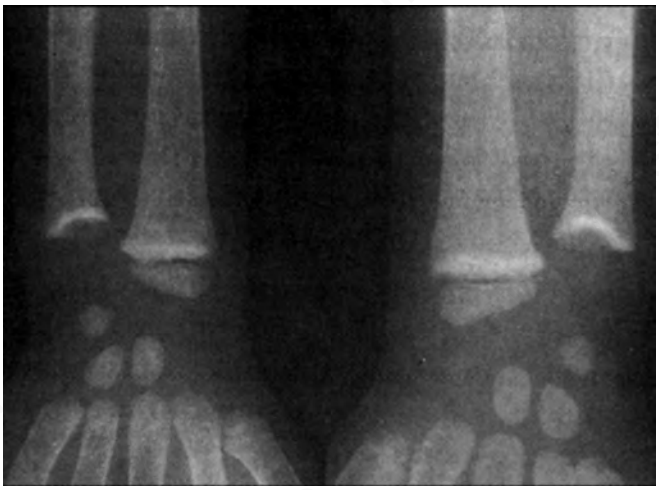


Fig. 1: Rickets. Widened and cupped epiphysis of the lower end of the radius

Management

A. ***Administration of vitamin D***

1. Ordinary case of rickets – 1200–2000 units per day.
   (a) *Fish oils* – Fish liver oils contain Vitamin D_3. The fat of the oil is a valuable addition to the diet.
      (i) Cod liver oil – 1 teaspoonful (containing about 400 units of vitamin D_3) three times a day. Some children do not tolerate it well and develop diarrhoea; older children may refuse on account of its taste.
      (ii) Halibut liver oil – 10 times more potent than cod liver oil.
   (b) *Vitamin D milk* – (i) Fortified milk. (ii) Irradiated milk standardised to contain 400 IV of vitamin D_3 per quart. The taste of the milk is not affected.
   (c) *Fortified fish oils* – Calciferol has been added to fish oils to enrich their Vitamin D content. The result is a product rich in both vitamin A and vitamin D. After healing has taken place it is necessary to continue with the dose during the second and third years of life.
   (d) *Exposure to sunlight* daily for at least 1–2 hours.
   (e) *Massive doses of vitamin D* (Stoss regime) – 600,000 IU of Vitamin D (15 mg calciferol) in oil solution intramuscularly or by mouth. Best current treatment of deficiency rickets. Advantages of Stoss regime – (i) Treats deficiency rickets with one dose, healing obvious on radiograph of wrist within 15 days. (ii) Differential diagnosis of deficiency and resistant rickets – 3 doses of massive D 15 days apart fail to produce healing in resistant rickets. (iii) Large dose prevents hypocalcemia during treatment.
2. Refractory rickets – Vitamin D dependent rickets – 40,000 units daily. Vitamin D resistant (hypophosphataemic) rickets – 400,000 units daily. Administration of neutral phosphate salts along with calciferol is helpful in healing rickets of VDRR type. Cause of refractory rickets should be established and treated.

   Hypervitaminosis D (more than 50,000–1,00,000 IU/day) Symptoms: Nausea, vomiting, constipation, abdominal cramps, and later muscular weakness or pain and dizziness, excessive thirst, polyuria, irritability, drowsiness, CKF.

   Diagnosis: Level of serum calcium and inorganic phosphorus rises and urine may contain calcium casts. X-ray of radius and ulna show deposits of calcium salts. Renal calculi. Metastatication in arteries and kidneys due to hypercalcaemia.

B. ***Calcium*** – Not usually necessary except in tetany. In acute convulsions 2 mL/kg calcium gluconate 10% IV. Maintenance 100-150 mg/kg of elemental calcium. Calcium lactate 300 mg = 40 mg (13%) of elemental Ca, calcium gluconate gives 9 mg elemental calcium per ml.

C. ***Use of cereals*** – in diet should be restricted because phytate of cereal combines with calcium to form an insoluble compound which is passed out in the faeces. Lactose is antirachitic.

SCURVY

Aetiology

Due to deficiency of vitamin C.

Age – usually from 6 months to 2 years.
Diet – more common in artificially fed infants.
Precipitated by febrile disease, infections, or diarrhoea.

Clinical Features

1. **Onset** – (a) Usually gradual – Fretfulness and increasing pallor, or tenderness of legs which causes child to cry whenever touched, anorexia and loss of weight. (b) Rarely sudden onset, the first symptom being inability of the child to use his legs.
2. **Symptoms due to haemorrhages:**
   (a) *Under periosteum of long bones* – "pithed-frog posture" with thighs flexed and abducted and knees flexed, sometimes diffuse swelling above or below the knee; in severe cases infiltration of muscles with blood causing oedematous limbs (woody leg); haemorrhage between diaphysis and epiphysis causes separation of epiphysis from shaft.
   (b) *In the gums* – only if teeth have erupted, common at base of incisors. In mild cases only a narrow line of purple discolouration, but in severe cases gums swell up into large, purple fleshy masses which bleed on touch, and teeth become loose.
   (c) *Perifollicular hemorrhage.*
   (d) *Within the orbit* – proptosis with swelling of eyelids.
   (e) *Haematuria* – May be an early symptom, often only microscopic.
   (f) *Scorbutic beading of the ribs* – due to backward displacement of sternum and costal cartilages, or sometimes due to haemorrhage at the junction of the ribs and cartilage; in contrast to rachitic rosary is sharp.

3. **Anemia**.
4. **Keratosis of hair follicles** with 'corkscrew' hair.
5. **Failure of wound healing**.

Diagnosis

(i) **Radiography**

Acute phase

- Generalized decrease in bone density of shaft and epiphyses (ground glass appearance).
- Pencilled cortex – Cortex is thinned out appearing only as a pencil streak.
- 'White lines of Frankel' – Thickening of provisional zones of calcification at epiphyseal ends of long bones, which become dense and cast heavy transverse shadow at the end of the shaft.
- 'Zone of Trummerfeld' – (a) A radiolucent area proximal to the white line due to atrophy of subepiphyseal cortex and spongiosa and which casts a narrow zone of rarefaction. This is a somewhat weak zone and leads to easy fractures and (b) Marginal metaphyseal infarctions, which during stages of healing protrude laterally to form Pelkan's spurs (Corner sign) (Fig. 2).
- Halo sign of Wimberger – due to pencilling effect produced by the epiphysis. Thus, the epiphysis is seen as a rim standing out against a rarefied body with pencilling resembling 'signet rings'.
- Subperiosteal hematomas – Soft tissue densities due to lifting off of the periosteum from the underlying bone (Figs. 3A and B).
- Joint effusions – causing bulging of joint capsule or the flat planes around the joint.
- Subluxation of epiphysis may occur in very severe cases.
- Scorbutic rosary – Step-like subluxation of costochondral joints.

Healing stage

- Cortex becomes thicker and rarefied transverse areas at the end of shafts regain normal density.
- In case of lateral displacement of the epiphyseal cartilage, a new shell of bone on the cortex aligns itself with the displaced epiphysis following treatment and there is no permanent deformity.
- The contour of the shaft returns to normal.

(ii) **Plasma ascorbic acid level** – very low.

Management

Vitamin C – (i) 3 to 4 ounces of fresh orange juice or tomato juice daily. (ii) Ascorbic acid – 100 mg or more orally or parenterally twice or thrice daily. Response dramatic. Pain lessens and alertness increases within 24 hours. X-ray changes take 15–21 days to resolve. Continue treatment for 10–15 days. IV vitamin C is mainly excreted in urine. Only used as test dose for relief of pain.

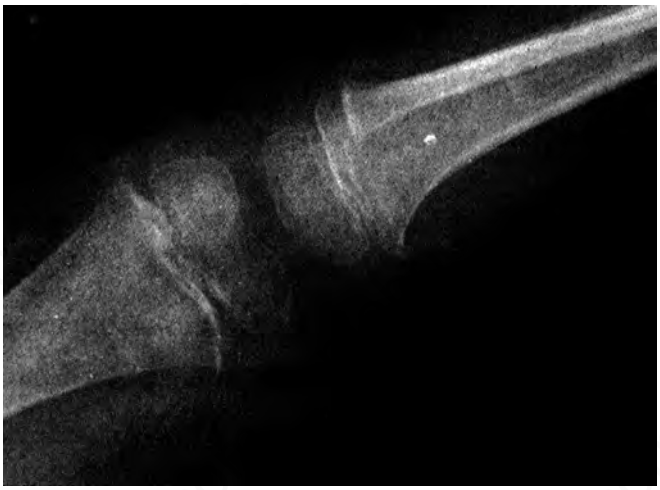
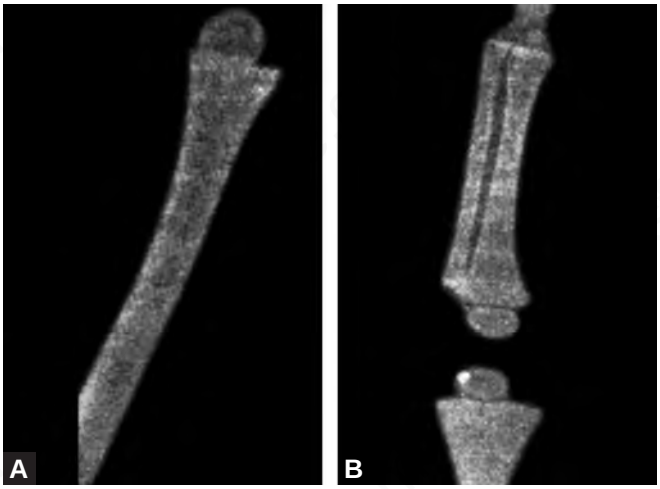


Fig. 2: Scurvy. Widening of the temporary calcification zone – 'the white line of scurvy'. Note the defect in the spongiosa and the cortex just below the epiphyseal plate. The 'corner sign of scurvy' and the spurs which have formed (Pelkan's spurs)



Figs 3A and B: Scurvy (A) Acute scurvy (tibia). Note white line at metaphysis surrounded by white ring, 'ground glass' appearance of shaft; (B) Healing scurvy (humerus). Club shape due to calcification of periosteal hematoma, and marginal metaphyseal infarction protruding laterally (Pelkan's spurs)

11. INFANTILE DIARRHOEA

Predisposing factors for acute diarrhoea – Infants under 1 year of age, bottle fed infants, poor hygiene, poor economic status.

I. **Infective diarrhoea** *See* Table 27 for the causative organisms.

Characteristics of diarrhoea caused by rotavirus:

1. Indistinguishable clinically from other causes of infantile diarrhoea.
2. Short incubation period (2-3 days).
3. Abrupt onset – Vomiting often precedes diarrhoea.
4. Illness usually lasts about one week, but usually improves within 2-3 days.
5. Temporary neutropenia may occur.
6. The illness may be very severe.
7. Hospital-acquired infection is common.

Pathophysiology of diarrhoea. *See* Table 28.

II. **Parenteral diarrhoea** – At onset of any acute infection, e.g. acute otitis media and mastoiditis, infection of respiratory tract, acute pyelonephritis and meningitis. Probably same virus involves both systems as in measles.

III. **Dietetic diarrhoea** – (a) Excessive quantity of food – overfeeding. (b) Excess of carbohydrates – Osmotic diarrhoea: loose, sour smelling stools. Lactase deficiency – Green, frothy, acid stools. (c) Allergy to certain foods or milk intolerance or milk protein allergy (more common with cow's milk). (d) Sucrose deficiency – Acid stools with RBCs.

If diarrhoea persists for more than 5 days, and if there is watery diarrhoea soon after introducing milk feeds, possibility of lactose intolerance, especially if abdominal distension soon after meals associated with perianal excoriation.

Table 27: Causative organisms of diarrhoea

Bacterial	*Viral*	*Parasitic*
E. coli (Diff. strains)	Rotavirus	Giardia lamblia
Clostridium difficile	Adenovirus	Entamoeba histolytica
Shigella	Others	Others
Salmonella (non-typhoidal)		
Yersinia		
Campylobacter		
V. cholerae		
Staphylococcal and others		

Symptoms

Mild case – Onset with loose diarrhoeal type of stools with sometimes vomiting. Gradual increase in frequency of stools; greenish, slightly offensive with mucus, varying in number from 2–3 to 10–12 per day. Slight fever.

Severe case – Onset moderately severe with or without vomiting. Stools soon become watery and odourless. Rapid dehydration as evidenced by thirst, dry tongue, depressed anterior fontanelle, loss of elasticity of skin and sunken abdomen. Fever, restlessness, tachycardia and oliguria. Later symptoms of toxaemia – apathy, staring sunken eyes, shallow respirations, uncountable pulse, cyanosis, acidotic breathing. Temperature high or sub-normal. "Cholera infantum" or acute toxic diarrhoea – In a very severe case rice water stools and symptoms of toxaemia. Abrupt onset with high fever and extreme prostration, vomiting, irritability, restlessness and often convulsions, collapse, suppression of urine and finally stupor and coma. Copious watery stool suggestive of toxigenic diarrhoea, small, frequent with tenesmus, blood and mucus in invasive infections – EIEC, Salmonella, Shigella, amoebiasis.

Table 28: Pathophysiology of diarrhoea

Character of stools	*Site of pathology*	*Likely organisms*
A. Large volume watery stools, macroscopic or microscopic blood/pus absent	Small intestine (Enteritis)	Viruses E. coli (EPEC, ETEC, EAggEC) V. cholerae Giardia
B. Frequent small volume stools, pus and/or blood present (naked eye/microscopy)	Large intestine (Colitis)	Shigella, E. histolytica E. coli (EHEC) (EIEC) Cl. difficile.
C. Initially large volume watery stools changing to small volume stools (Macroscopic or microscopic blood/pus present)	Small and large Intestines (Enterocolitis)	Salmonella Campylobacter Shigella sonnei
D. Stool type: Bloody	Acute dysentery Intussusception Ischaemic colitis Pseudomembranous colitis	
Nonbloody	Mostly small bowel diarrhoea	Bacterial, viral

Clinical assessment of dehydration in infancy – *See* Table 29.

Management

1. Fluids:

   (a) **Solution used** – (i) Ringer lactate – Full strength 1 ampoule in 500 mL glucose or 1/2 strength. (ii) Isolyte M is suitable rehydrating fluid in infants. (iii) Glucose-saline IV – 1/5th in newborns, 1/3 in older children, use after initial rapid rehydration. (iv) Potassium chloride (1 mL = 2 mEq), add 1 mL of solution to 100 mL IV solution (maximum 2 mL) after patient starts passing urine.

   (b) **Quantity** – (i) *Assessment of fluid loss* – According to grade of dehydration. In a moderately severe case there is a deficit of 100–120 mL per kg body weight. The aim of treatment is to restore the fluid deficit and to provide a maintenance intake according to the table. Volume of fluid lost through urine and stool is added to subsequent intake.

   (ii) Assessment of type of dehydration by estimation of serum electrolytes (see Table 31)

   Oral rehydration therapy – WHO solution formula (Table 32).

   Dissolve in one litre of potable water. Can be given by mouth or by Ryle's tube. Very useful in all cases of childhood gastroenteritis including cholera (Table 33). Based on the concept that glucose stimulated sodium absorption is intact in toxigenic diarrhoea, works in other forms. Contraindicated in severe dehydration with shock, paralytic ileus, persistent vomiting.

   Deficit is to be replaced in first 6-8 hours. Mild to moderate vomiting is not a contraindication to successful use. Vomiting can be controlled by Domperidone orally (0.5 mg/kg/day) which has no neurological side effects. Maintenance plus ongoing losses replaced thereafter over 18 hours in proportion of two feeds ORS to one feed milk.

Table 29: Clinical assessment of dehydration in infancy

Loss of wt.	*Cl. Fs.*
Mild (0.5%)	Thirst Dry mucous membranes Depressed fontanelle Normal pulse
Moderate (5–10%)	Markedly depressed fontanelle Loss of skin turgor Sunken eyes Tachycardia Oliguria
Marked (10%)	Increased severity of above signs Agitation or drowsiness Signs of shock

Table 30: Maintenance fluid requirements in children

Wt.	*Daily requirement*
3–10 kg	100 mL/kg
10–20 kg	1000 mL+50 mL for each kg. above 10 kg
> 20 kg	1500 mL + 20 mL/kg for each kg above
	20 kg

Table 31: Assessment of type of dehydration

Type	*Deficit*	
	Sodium	*Potassium*
Isonatraemic	8–10 mEq/kg	8–10 mEq/kg
Hyponatraemic	10–12 mEq/kg	8–10 mEq/kg
Hypernatraemic	4 mEq/kg	5–8 mEq/kg

Table 32: WHO ORS formula

Constituents (g/litre)	
Sodium chloride	3.5 gm
Sodium bicarbonate	2.5 gm
Potassium chloride	1.5 gm
Glucose	2.0 gm
Concentration (mmol/litre)	
Sodium	90
Chloride	80
Potassium	20
Bicarbonate	30
Glucose	110
(Recently sodium bicarbonate has been replaced by 2.9 gm sodium citrate and has better shelf-life).	

Table 33: Use of ORS

Grade of dehydration			
Stool output	*Mild*	*Moderate*	*Severe*
< 1 every 2 hours	50 mL/kg	100 mL/kg	100–120 mL/kg
> 1 every 2 hours	50 mL/kg	Replace at	10–15 mL/kg/hour

Sugar-based ORS – 40 g sugar (sucrose) replaces 20 g of glucose. Cheaper and as efficacious.

Rice-based ORS – Amino acids in rice exert separate water and sodium reabsorptive influence. Better than standard ORS by 40% rehydration efficacy.

Amino acid-based ORS (Super ORS) – Addition of dipeptides glycine-glycine or glycine-alanine improves sodium reabsorption.

Home-based ORS – using hand measures or special spoons. 4 glasses of water plus 4 finger scoops of sugar plus 3 finger pinch of salt. Squeeze of lime adds some potassium and flavour. Must taste like tears.

2. **Diet** – Solid feeds must be given during diarrhoea to prevent PEM. Clear fluids containing electrolytes in first 24 hours. After 24–36 hours, weak milk mixture may be substituted. Homemade butter milk can also be used.
   Mashed rice, curds and dal safely given.
3. **Feeding of breast milk** – must continue.
4. **Antimicrobial drugs** – Indications – (a) Blood and mucus in stool. (b) Faecal leucocytes 20–25/hpf. (c) High fever. Start with – (i) In newborns – Parenteral Ampicillin 100 mg/kg/day IV 6–8 hourly for 5–7 days, or Gentamycin 5 mg/kg/day 12-hourly or Colistin 6–8 mg/kg/day in 3–4 divided doses for 5 days. (ii) Older children – One of the following for 3 days – Cotrimoxazole – 10 mg/kg/day of Trimethoprim in 2 divided doses. (d) Furazolidone – 6–8 mg/kg/day in 2–3 doses. (e) Ampicillin – 50–100 mg/kg/day in 2–3 doses. (f) Norfloxacin 10 mg/kg/day in two or Ciprofloxacin 20 mg/kg/day in two divided doses. (g) Nalidixic acid – 55 mg/kg/day in 3–4 doses. Excellent response to invasive infections. (h) Erythromycin 40 mg/kg/day for Campylobacter infections. (i) For E. histolytica – Metronidazole or Tinidazole 40 mg/kg/day in 3 divided doses for 7–10 days. (j) For giardia – Metronidazole 15–20 mg/kg/day for 5 days, or Furazolidone.
5. Severe dehydration – *IV fluid therapy* – Ringer's lactate, or if not available N saline. (a) Age – < 12 months 30 mL/kg in 1hr followed by 70 mL/kg in 5 hours. (b) 12 months – 5 years: Same quantities in 30 minutes and then after 2½ hrs. Sodium losses in severe dehydration 10–12 mEq/kg. After electrolytes estimation, replace Na^+ deficit at (Na expected – Na observed) × 0.6 × body wt (kg). This is added to maintenance Na^+ need of 2–3 mEq/kg/day. Potassium losses 8–10 mEq/kg in severe dehydration. Start adding K^+ to drip once urine output is established, can be dangerous and cause paralytic ileus.
6. Binding agents and anticholinergic drugs – not recommended. Some secretory diarrhoeas respond to Loperamide or Aspirin (25 mg/kg), the latter has antiprostaglandin effect. Not to be used routinely in infective diarrhoeas.

Persistent diarrhoea (PD) – Acute diarrhoea which lasts for at least 14 days. The main causes are (excluding conditions such as coeliac disease, metabolic or biochemical disorders):

1. Persistent infection with one or more enteric pathogens.
2. Malabsorption particularly of carbohydrates and fats
3. Rarely dietary protein intolerance.

Complications

Dehydration – if reduced, oral intake. Growth retardation and worsening of malnutrition. It may prove fatal during subsequent diarrhoeal or non-diarrhoeal illness.

Management

Dietary management is the mainstay of therapy.

Infants < 4 months – (a) Exclusive breastfeeding. (b) If only top milk is given, use curds or lactose-free milk formula. (c) From 3rd month onwards, cooked rice can be mixed with milk/curd/lactose-free formula.

Older infants and young children – Breast milk output becomes less and mixed diet should be given.

12. ACUTE GASTROENTERITIS IN CHILDREN

Table 34 gives causes and Table 35 risk factors of acute gastroenteritis in children.

13. PICA

The term 'pica' is derived from a Latin word for magpie a bird known for its eating behaviour. The diagnostic and statistical Manual of Mental Disorders (DSM-IV) defines pica as the persistent eating of non-nutritive substances for a period of at least one month without an association for aversion of food.

Physiological basis for various forms of pica-eating clay (geophagia), ice (pagophagia) or starch (amylophagia) is not well understood.

Table 34: Causes of acute gastroenteritis in children

Viruses 70%
• Rotavirus
• Norovirus (Norwalk-like virus)
• Enteric adenoviruses
• Calci viruses
• Astroviruses
• Enteroviruses
Protozoa 10%
• Cryptosporidum
• Giardia lamblia
Bacteria 10–20%
• Campylobacter jejuni
• Salmonella spp. Non-typhoid
• Enteropathogenic E. coli
• C. difficile
• Shigella spp.
• Yersinia enterocolica
• Salmonella typhi and S. paratyphi
• Vibrio cholerae
Helminths
• Strongyloides stercoralis

Table 35: Risk factors for AGE

• Environmental contamination
• Immune deficiency
• Measles
• Malnutrition
• Lack of exclusive breastfeeding
• Malaria
• Zinc and vitamin A deficiency

Table 36: Viral and bacterial gastroenteritis differentiation

Feature	*Viral*	*Bacterial*
Season	Year-round	More common in summer and rains
Reservoir	Primary human	As per species: Human (Shigella, Salmonella), Animal (Campylobacter, salmonella, E. coli), Antibiotic use (C difficile) water (V. cholerae)
Fever	Common with rotavirus, norovirus	Common with inflammatory disorder (Shigella, salmonella)
Vomiting	Can be the only presenting feature in children	Common with bacteria producing preformed toxin
Diagnosis	Enzyme immunoassays for detection of rotavirus and adenovirus	Stool examination for pus cells, RBCs Stool culture on special media
Treatment	Supportive therapy Antibiotics contraindicated	Oral hydration therapy Antibiotics Anti-secretory agent: Racecadotril or Octreotide (single dose)

Table 37: Assessment and management of dehydration

Dehydration	*Clinical signs*	*Pinch test*	*Management*
Nil Mild to moderate 5–10% wt. loss	None 2 or more of restlessness, irritability, sunken eyeballs	Normal Slow (Skinfold visible < 2 secs)	Normal diet without breastfeeds Can be managed at home with oral dehydration therapy. If not tolerated then NG feeding or IV fluids
Severe > 10%	2 or more of abnormally sleepy, sunken eyes, drinking poorly	Very slow (> 2 secs)	Check acid-base status, urea, electrolytes before IVF. If shock, resuscitate with IVF rehydrate 4–6 hrs. Regular clinical and biochemical review

During infancy, this habit may be a part of oral phase (normal exploration of the environment).

Predisposing factors:

- Mental retardation
- Lack of parental nurturing
- Children with autism
- Brain-behaviour disorder
- Low socio-economic groups
- Iron deficiency
- Lesch-Nyhan syndrome.

Complications of pica include:

- Heavy metal poisoning
- Metabolic abnormalities
- Intestinal obstruction
- Nutritional deprivation
- Worm infections
- Increased risk of Alzheimer's disease

Substances eaten:

Wall plaster
Clay
Earth or mud
Pencil
Lead
Paint
Ash
Cigarette buts
Soap

Management: Screening for lead poisoning, iron-deficiency anemia, parasitic infestation.

14. INDIAN CHILDHOOD CIRRHOSIS (ICC)

Aetiology: (a) *Incidence* – Disease peculiar to Indian subcontinent with 80% of all cases of cirrhosis in India. Incidence has come down significantly in recent years. (b) *Age* – from 1 to 3 years usually, may occur in older children also. (c) *Sex* – Apparently more common in males, usually first male child after many females. (d) *Familial incidence*– known but definite inheritance not defined. (e) *Community* – Mainly Hindus. Common in Agarwals and Banyas (North India) and Brahmins of South India.

AETIOPATHOGENESIS

Appears to be a response of a genetically inferior liver to viral infection. Theories:

1. *Nutritional* – Seen in traditional vegetarians. Rare in poor and malnourished, commoner in middle income groups. No dietary deficiency appears to contribute. Excessive intake of copper may have a role from use of copper and brass vessels for cooking and storing water.
2. *Viral infection* – appears logical because of febrile onset and leucocytosis. 20% of ICC patients have recent family history of viral hepatitis. Hepatitis B antigen found in 5–20% of cases. However, there is no increased incidence of the disease following epidemics of viral hepatitis.
3. *Genetic* – Siblings can be affected; reported in many generations and in twins. Abnormal palm print patterns have been noted.
4. *Toxic* – Aflatoxin more in urine of patients with ICC and in breast milk of their mothers. Herbal medicines containing toxic levels of arsenic used by mothers in pregnancy "to change sex of child" have been implicated. High levels of copper demonstrated in liver. High copper intake of diet implicated especially in top fed babies where milk is boiled in brass or copper vessels. Patients have been also found to have zinc deficiency.
5. *Immunological* – Could be an autoimmune disease, autoliver antibodies against antigenically altered liver cells by virus. Also evidence of primary defect in cell-mediated immunity has been found.

PATHOLOGY

Liver remains enlarged throughout illness, may shrink slightly in terminal stages. Organ surface finely granular, hard consistency. On microscopy early changes– ballooning of cells; later stages – necrosis with reticular system collapse, hyaline material (Mallory bodies) seen; no fatty change, "creeping fibrosis", no bile duct proliferation and hardly any regeneration.

CLINICAL FEATURES

Onset – usually insidious. In some, acute onset with fulminant fatal course. The disease ultimately proves fatal within one year of diagnosis.

Early stage – There may be history of infective hepatitis. Child becomes irritable, is off-colour and does not play. Diarrhoea with sticky stools, episodes of low grade fever, flatulence, peevishness, excessive crying and inability to thrive are common complaints. The liver is just palpable and firm with a sharp margin. The spleen may become palpable. These symptoms are referred to as 'pre-cirrhotic symptom complex'.

Intermediate stage – Clinical features more definite. The child looks very ill and may be frankly jaundiced. Abdomen becomes more prominent and dilated superficial veins become visible. A hard liver is always palpable and has a leafy edge and also the spleen owing to development of portal hypertension. Oedema of ankles. Some puffiness of face and ascites may appear.

Terminal stage – The child has deep icterus and the abdomen becomes protuberant with liver enlarged up to umbilicus and spleen becoming hard. Marked ascites. Child may die of hepatic coma, intercurrent infection or bleeding episode.

LABORATORY FEATURES

(1) Leucocytosis. (2) Urinary glycosuria. (3) Increased conjugated bilirubin. (4) Elevated alkaline phosphatase. (5) Decreased serum albumin (later). (6) Increase in gamma globulins, mainly IgM. (7) Decreased serum complement. (8) Impaired tests of cell mediated immunity. (9) Positive Australia antigen in few cases. (10) Increased serum free copper, urinary copper. (11) Miscellaneous – Increased alfa fetoprotein, low alpha-1-antitrypsin, low serum zinc, excess liver copper. (12) Liver biopsy – shows Mallory bodies and increased concentration of copper.

MANAGEMENT

I. **General** – (1) *Diet* – Balanced diet in compensated state. Salt restriction, protein supplements with additional

glucose in presence of oedema and ascites. Protein restriction (1 g/kg/day) in hepatic coma. (2) *Vitamins* – specially A, D and E orally. Vitamin K 5 mg IM for 3 days if there is bleeding. (3) *Diuretics* – Spironolactone 2 mg/kg/day or Frusemide 2 mg/kg/day if oedema and ascites, with oral potassium chloride. (4) Treatment of hepatic coma – IV glucose, protein restriction, oral neomycin, high bowel washes, treatment of infection. (5) Liver extracts, vitamin B_{12} of no therapeutic value.

II. **Specific** – None of the therapies of proved value. (1) *Steroids* – Prednisolone 1–2 mg/kg/day for 2–3 weeks followed by half the dose on alternate days for several months if improvement seen. (2) *Gamma globulin* – 0.1–0.3 mL/kg IM every 3 weeks for 1–2 years has been used with some benefit. (3) *L-tetramisole* – a drug stimulating cell mediated immunity has not proved of value. (4) *Copper chelating agents* – Penicillamine 20 mg/kg/day for periods up to 6 months may bring about reversal of pathological changes in liver. (5) *Zinc therapy* – 30–120 mg/day. Some have claimed improvement.

Prognosis – 45% die in 1 month, 75% in 2 months and 85% in 6 months after diagnosis.

Prevention – Early cases detected by palpating livers of 6 months to 3-year-old siblings of patients. Penicillamine in these cases is not effective because the fibrosed liver has poor capacity for regeneration. Avoid use of copper and brass vessels.

15. WHEEZING INFANT

Wheeze is a symptom and not a diagnosis. It is quite common in children and a number of them have commonly experienced recurrent episodic wheezing. Wheezing results from widespread peripheral airway narrowing.

RISK FACTORS

- In infants, wheezing may be due to exposure to environmental tobacco smoke during foetal life and postnatally
- Viral infection
- Atopy may be implicated in children with severe disease
- Brief or no breastfeeding during the first few weeks of life increase the risk of wheezing in infancy, possibly because of reduced protection against viruses.

Pathogenesis – Acute episodes of wheezing in infancy are characterized by hyperinflation and an increase in airway resistance. In infants, there is little bronchodilator response to b_2-agonists given by aerosol. As b_2-agonists block the action of nebulized bronchoconstrictor agents during bronchial challenge in infants.

Table 38: Uncommon causes of chronic or recurrent wheezing in infants

Developmental anomalies
• Bronchomalacia (localized or generalized) and tracheal anomalies
• Bronchial compression syndromes (e.g. vascular anomalies, bronchial or pericardial cyst)
• Congenital heart disease (left-right shunts)
• Tracheal granuloma, stricture or polyp (after mechanical ventilation)
Host defence defects affecting the airways
• Cystic fibrosis
• Ciliary dyskinesia
• Defects of immunity
Postviral syndromes
• Obliterative bronchiolitis
• Airway stricture or granuloma
Recurrent aspiration
• Gastro-oesophageal reflux
• Disorders of swallowing (neuromuscular disease)
• Tracheo-oesophageal fistula
• Laryngeal cleft
Perinatal inflammatory lung disease
• Chronic lung disease of prematurity
• Congenital infection

CLINICAL FEATURES

There are two main patterns:

- Acute episodic wheeze and cough are commonly associated with respiratory viral infection and punctuated mainly by symptom free intervals. Rhinoviruses, RSV, coronaviruses and metapneumovirus are commonly implicated.
- Chronic symptoms include day-to-day wheeze and troublesome, dry night-time cough. Acute episodes may also occur. There may be atopic features.

DIFFERENTIAL DIAGNOSIS

- Perinatal respiratory disease or neonatal symptoms
- Extreme prematurity
- Vomiting, posseting or dysphagia

- Inspiratory noises or expiratory noises other than wheeze. Other features that indicate alternative diagnosis or major complications include:
  - Persistent failure to thrive
  - Hypoxia between episodes
  - Focal signs on auscultation
  - Inspiratory wheeze or stridor
  - Abnormal voice or cry

INVESTIGATIONS

- Chest radiograph
- CT scan to exclude structural disorders such as airway compression
- Bronchoscopy if bronchial stricture or foreign body is suspected
- Sweat test if cystic fibrosis is suspected
- 24-hour oesophageal pH study for GER
- Oximetry to monitor arterial O_2 saturation during acute episodes. SaO_2 < 92% during quiet sleep, or a quiet awake state suggests airway obstruction requiring hospitalization.

MANAGEMENT

(a) Avoidance of trigger factors, cigarette smoke being the most important. (b) Overcrowding in presence of older siblings in day nurseries increases risk of viral infections in infancy. (c) Breastfeeding reduces risk of wheeze. (d) Drug treatment – (i) Bronchodilators – inhaled b_2 agonists may be more effective when given by metered dose inhaler and spacer than by jet nebulizer. (ii) Corticosteroids – Infants with chronic symptoms (between and during viral episodes) benefit from long-term prophylaxis with inhaled corticosteroids. (e) Mechanical ventilation may be needed, if exhaustion or a gradual increase in oxygen requirement occurs. $PaCO_2$ is seldom used as a single indicator of the need for ventilatory support in infancy. The efficacy of treatment increases with age and when intercurrent symptoms accompany acute wheezy episodes.

16. BRONCHIOLITIS AND BRONCHOPNEUMONIA

Bronchiolitis and Bronchopneumonia are the most serious respiratory illnesses in childhood involving the airways because of (a) Smaller airways which easily get obstructed by inflammatory oedema or secretions. (b) Airway resistance. (c) Marked chest wall recession. (d) Immature respiratory muscles leading to rapid muscle fatigue.

Bronchiolitis is an inflammation of the bronchioles caused mainly by viruses, the most common being respiratory syncitial virus, but also human parainfluenza virus type 3, and some adenoviruses.

Predisposing factors – Weak and marasmic children, rickets, or infective fevers like measles and whooping cough. Viral bronchitis occurs in healthy children 3 months to 9 months old. In children with allergic diathesis, any respiratory infection can trigger off bronchiolar spasms.

PATHOGENESIS

Acute bronchiolitis – in the first 6 months of life is an inflammatory disorder characterized by a massive influx of neutrophils into the lung.

Bronchopneumonia – The interalveolar connections (pores of Kohn and canals of Lambert) are poorly developed in small infants so that contiguous spread to nearby areas is not possible. Hence, infection reaching the alveolus can produce localized exudation and consolidation but is unable to spread to the adjacent alveoli; as a result, confluent areas of consolidation cannot develop and bronchopneumonia and not lobar pneumonia is the usual feature in infants.

SYMPTOMS

1. Onset – Acute with fever, and often vomiting and convulsions; or after preceding nasal or pharyngeal inflammation or tracheobronchitis.
2. Fever – rises rapidly to 39°C (103°F) or more and may remain continuously high in bronchopneumonia. In bronchiolitis, fever may be minimal and in allergic bronchitis, it may be totally absent. More often gradual rise with a tendency to remittance may be of "saw tooth" variety. In debilitated children, normal or subnormal temperature. Fever falls by lysis. Remissions and relapses may carry the disease over a period of 3–4 weeks.
3. Dyspnoea – constant symptom. Very acute and progressive and with sudden subsidence with bronchiolitis. Bronchopneumonia is progressive if untreated, bronchiolitis may reverse with simple measures.
4. Cough and wheeze – since the bronchus and smaller airways are infected, there is irritation of the airways. Hence, a dry cough is a predominant symptom accompanied by wheezing in bronchopneumonia. Children under 4 years cannot expectorate.

5. Cyanosis – may be an early symptom.
6. Prostration – to some extent in all cases, in bad cases, child lies exhausted with half open eyes.
7. Gastrointestinal symptoms – common in infants, vomiting occasional or repeated. Diarrhoea may occur at onset.
8. Neurological – Convulsions may occur at onset or later may indicate meningitis. General restlessness and delirium. Insomnia, or apathy and stupor, or even coma.

SIGNS

1. *Respiration* – Respirations are rapid and shallow and often accompanied by a respiratory grunt. The accessory muscles of respiration are used actively so that there is suprasternal and subcostal indrawing with inspiration.
2. *Chest* – In bronchiolitis, physical findings in the severe case are those of generalized obstructive emphysema. Cyanosis may be striking and often there is extreme pallor. The percussion note is hyperresonant. There may be prolonged expiration with wheeze, but may have no signs at all except decreased air entry bilaterally. Liver and spleen palpable due to diaphragm being pushed down. Coarse crackles are heard all over in bronchopneumonia.
3. *Dehydration* – may be relatively severe due to excessive loss of water through hyperventilation.
4. *X-ray* – examination may reveal generalised obstructive emphysema of varying degree with or without evidence of scattered parenchymal infiltration in acute bronchiolitis. In bronchopneumonia lesions diffuse and are bilateral. Diffused lesions mimic miliary TB. Confluent areas of bronchopneumonia may simulate lobar pneumonia. Staphylococcal – breaking down and cavitary lesions seen which heal as thin-walled sacs (pneumatocoeles) which persist quietly for a year.

MANAGEMENT

1. *Nursing* – Good nursing essential to conserve child's energy.
2. *Diet* – should be as normal as child will accept.
3. *Sedatives* – to be used judiciously, may be indicated if restlessness is distressing but this may be due to hypoxia which only a high concentration of O_2 will relieve. Best sedative to control excessive crying and exhaustion which will not cause respiratory depression is Chloral hydrate 50 mg/kg.
4. *Antibiotics* – Crystalline penicillin 1.4 lakh unit's kg/IV 6-hourly, or Ampicillin 100 mg/kg/day, in divided doses 6–8 hourly. Amoxicillin clavulanic acid combination – Amoxicillin 30–40 mg/day in 3 divided doses, IV cephalosporins (2nd and 3rd generation) very useful. If due to staphylo. cloxacillin 100–200 mg/kg IV 6-hourly. The course of virus disease will not be altered but secondary infection will be controlled. Vidarabine 10 mg/kg/day IV is useful for treating RSV infections in high-risk groups, such as cyanotic heart disease.
5. *Symptomatic treatment* –
   (a) *Bronchodilators* – Salbutamol aerosol 0.03 mL/kg empirically. Nebulized racemic epinephrine 1 mL/kg diluted with normal saline more effective.
   (b) *Cyanosis* – Humidified oxygen, with blood gas monitoring. Sodium bicarbonate if significant metabolic acidosis.
   (c) *Fever* – Paracetamol may be used.
   (d) *Fluids* – Parenterally if respiratory rate more than 60/minute. Weaned off to oral feeds with decreasing distress. Necessary to correct dehydration due to tachypnoea and prevent aspiration.
   (e) *Steroids* – Value not proven in bronchiolitis. Not to be used in bronchopneumonia.

17. ACUTE RHEUMATIC FEVER

Acute rheumatic fever is initiated by group A streptococcal pharyngitis. This is followed by a latent period of 2–6 weeks, after which the clinical syndrome of acute rheumatic fever evolves characterized by:

- Polyarthritis
- Carditis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

These features may occur singly or in any combination.

AETIOLOGY

Predisposing causes – *Age* – 5–15 years. *Sex* – equal incidence, later in boys. Chorea more in females. Also MS more in females. AR in males. *Genetic factors* - Familial incidence known. *Social and economic factors* – Dampness, overcrowding and undernutrition greatly increase the incidence. *Idiosyncrasy* – is presumably a factor, since only 3% of people involved in streptococcal epidemics develop rheumatic fever. These susceptible individuals include a

significantly higher proportion of non-secretors of ABC blood groups. HLA associations being shown along with other immune markers to explain susceptibility.

PATHOGENESIS

Rheumatic fever is invariably preceded by infection with a group A beta-haemolytic streptococcus of specific M-types. Serum from patients with ARF contains antibodies to an antigen in the membrane of the organism, the type 5 streptococcal in protein, which cross-reacts with myocardial tissue. Similarly between streptococcal cell wall antigen and endogenous antigens in cardiac tissue, synovium, cartilage and brain lead to immunologic attack by the host antibodies and manifestations of acute rheumatic fever.

CLINICAL FEATURES

(a) *Prodromal phase* – Tonsillitis or sore throat 1–4 weeks prior to onset of acute rheumatic fever. Vague prodromata include "Growing pains", anorexia, pallor, fatigability and nervous irritability, and low grade febrile attacks.

(b) *Latent period* – when antibodies to the preceding streptococcal infection are produced. May vary in length from a few days to several weeks.

(c) *Phase of onset* – of acute rheumatic fever.

Modes of onset –

(i) Arthritis and fever 2–3 weeks after infection. (ii) Cardiac symptoms 3–6 weeks after infection may be the first to draw attention, e.g. pain of pericarditis, or palpitation, or symptoms of cardiac failure. (iii) Abdominal symptoms – abdominal pain and tenderness, nausea, vomiting, fever and leucocytosis simulating an acute abdomen. (iv) Pyrexia of unknown origin. (v) Typhoid or influenzal mode of onset with fever, toxaemia and vague abdominal or respiratory symptoms. (vi) Chorea may be the first and only evidence 6 months-1 year later. (vii) Latent valvular disease without previous history of rheumatic fever. (viii) Nodules, or skin lesions, or epistaxis may rarely be the first symptoms.

SYMPTOMS AND SIGNS

1. ***Polyarthritis*** – Pain disproportionate to objective joint findings. Joints most subject to stress and strain first affected. Migratory or flitting signs of acute inflammation but no suppuration Polyarthritic form is divided into –
   (a) *Monocyclic* – single cycle of fever for 10 to 15 days, each joint inflamed for 4 to 6 days, recovers and is not again affected.
   (b) *Polycyclic* – joints which have recovered again get involved. Recurrence of arthritis and fever as soon as influence of drug wears off.
   (c) *Continuous form* – persistence of some evidence of active infection often varying in intensity from time to time.

   Jaccoud's arthritis – is a rare sequel to repeated attacks of acute rheumatic fever. The features are – (a) Hands and feet are affected. The typical deformity of hands is of marked ulnar deviation of ring finger and slight ulnar deviation of other fingers. (b) Absence of pain. (c) Periarticular fibrosis. (d) Effusions rare, when present seen in metacarpal heads. (e) Tests for rheumatoid factor negative and ESR normal.
2. ***Fever*** – is usually low grade and never the presenting symptom. Almost always present. Types – (i) Irregular but well-marked. The temperature may rise to 101–103°F, shows daily variations of 1–3°F. Duration variable, may last from a few days in mild cases to a few weeks in severe attacks. (ii) Continuous low grade fever. (iii) Continuous low grade fever with acute exacerbations during relapses. (iv) Hyperpyrexia may rarely occur with delirium, convulsions, and coma.
3. ***Carditis*** – Rheumatic carditis is an acute inflammatory process that may involve the endocardium, myocardium or pericardium and frequently a combination of all three.

   Endocarditis – or valvulitis is indicated by the presence of a significant heart murmur not previously noted – (a) *Systolic murmur* of mitral regurgitation may be heard early in the course of the illness. (b) *Carey Coombs murmur* – Mid-diastolic murmur localized at the apex due to acute mitral valvulitis. It may be transient. (c) *Basal diastolic murmur* of aortic regurgitation due to acute involvement of aortic valve may be heard. The murmur of MR is more likely to disappear whereas the murmur of acute AR usually persists. A mitral stenotic murmur develops only some years after acute episode of rheumatic fever. Tends to be seen earlier in Indian populations. Order and frequency of valvular involvement – commonest mitral, then aortic, tricuspid and pulmonary.

   Myocarditis – is suggested by – (a) Tachycardia disproportionate to the fever. (b) Decrease in intensity of 1st heart sound indicating first degree A-V block. (c) Diastolic gallop rhythm or early signs of failure (such as tachypnoea and shortness of breath).

   Pericarditis – occurs in patients with severe carditis and is indicated by a friction rub. Large pericardial effusion is uncommon.

4. ***Chorea*** can occur alone (pure chorea) or in association with carditis. The latent period between the streptococcal infection and onset of chorea is characteristically long (2–6 months), this accounts for the normal ESR and antistreptolysin-O (ASO) titres that are usually found in patients with chorea. Chorea is more common in girls than in boys and usually occurs at the age of 8–12 years. The symptoms lasts for 3–4 months, sometimes longer.

   Emotional liability requires a high index of suspicion. School teachers and parents may observe that the child prefers to be alone, is mildly depressed, has a short attention span and is easily provoked.

   Involuntary movements principally involve the face and may be unilateral.

5. ***Skin*** –
   - *Erythema marginatum* – most characteristic lesion. May occur 3 weeks after infection. Pale-centred ringlets with pink margins, over trunk and flexure surfaces of joints. There may be few lesions or many, usually evanescent. As a rule, it is recurrent and may appear from time to time long after other manifestations have subsided.
   - *Erythema multiforme* – fairly common.
   - *Erythema nodosum* – Nodular eruptions usually on the legs. The lesions are tender and warm. Cropping of the lesions is common.
   - *Purpuric eruptions* may rarely occur.
   - *Sudaminal eruptions* due to marked sweats is an early manifestation along with arthritis.

6. ***Subcutaneous nodules*** – (i) Painless, translucent, non-pruritic, conical or rounded nodules just under the skin, varying in size from a pinhead to about 2 cm in diameter. Appear in crops on extensor surface of elbows, dorsum of hand or foot, skull, scapula and other bony prominences. Sign of virulent process. Occur relatively late (6 weeks to 6 months) in the course of the disease and remain for several weeks. (ii) Rheumatic tendinitis, tenosynovitis, myositis and bursitis may seldom occur. Nodules indicate chronicity, and are associated with significant heart disease.

7. ***Respiratory*** – (i) Epistaxis may be an atypical manifestation. (ii) Rheumatic pneumonia – uncommon and almost always occurs in patients with severe carditis. Chest X-ray may show changing areas of pulmonary infiltration which do not respond to antibiotics but respond dramatically to steroid therapy.

8. ***Gastrointestinal*** – (i) Mild gastroenteritis may be one of the prodromal features. Occasionally signs of acute appendicitis due to inflammatory changes in the right rectus abdominalis muscle, or to inflammatory changes in the mesentery, or to enlargement of abdominal lymph glands. (ii) Repeated vomiting spells.

LABORATORY FINDINGS

1. Evidence of preceding streptococcal infection – Antistreptolysin-O (ASO) determination useful in 80 per cent of cases. Titre < 250 considered normal, 250–320 borderline elevated. Eighty per cent of rheumatic fever patients have higher than 250 units/litre, of which 60% are above 500 units. Serial rises more significant. Antistreptozyme test (ASTZ) – Tests for 5 streptococcal enzymes antigenically more accurate diagnostically. The titre usually rises within 1–2 weeks and increases until a maximal level is reached 3–5 weeks after infection, returns to normal in 8–16 weeks.

2. Acute phase reactions – not specific for rheumatic fever. (a) *ESR* – elevated. (b) *C-reactive protein* – reflects rheumatic activity more precisely than ESR. (c) *Serum proteins* – Significant elevation of serum haptoglobin common in acute phase.

3. Miscellaneous:
   (a) *Anaemia* – mild to moderate. Persistence of anaemia is often a sign that rheumatic inflammation is still present.
   (b) *ECG* – (i) Disturbance of conduction – Prolonged PR interval or more severe grades of heart block. (ii) Changes associated with myocarditis. (iii) Abnormalities secondary to pericardial involvement.
   (c) *X-ray chest* – Cardiac enlargement may help to confirm diagnosis of carditis in equivocal cases.

Table 39: Revised Jones criteria

Major criteria	*Minor criteria*
Carditis	*Clinical:*
Polyarthritis	Fever
Erythema marginatum	Arthralgia (esp. if there
Chorea	is major arthritis).
Subcutaneous nodules	Previous rheumatic fever or RHD.
	Laboratory:
	Raised – ESR,
	leucocytes, C-reactive protein.
	Prolonged PR interval on
	ECG (not if there is major carditis).

Two major manifestations or one major with two minor manifestations in the presence of evidence of previous streptococcal infection makes the diagnosis of rheumatic fever highly probable.

WHO Recommendations

- Chorea and indolent carditis do not require evidence of antecedent Group A streptococcus infection or other major criteria.
- First episode as per Jones criteria
- Recurrent episode:
  - In a patient without established RHD, as per first episode
  - In a patient with established RHD requires two major manifestations plus evidence of antecedent Group A streptococcus infection as per Jones criteria.

WHO criteria can be used for both first episode and recurrent episodes of acute rheumatic fever. Supporting evidence of preceding streptococcal infection also includes positive rapid antigen test for Group A streptococci on sore throat.

Chorea alone, insidious or late onset carditis with no other explanation can be indicative of disease without evidence of preceding streptococcal infection. In those with documented rheumatic heart disease, presence of one criterion, or of fever, arthralgia or elevated acute phase reactants is presumptive diagnosis of recurrence.

DIFFERENTIAL DIAGNOSIS

1. *Juvenile rheumatoid arthritis* – (Still's disease) – may present with acute arthritis with history of preceding sore throat. Points in favour of Still's disease are high swinging, intermittent temperature as compared with the more persistent or remittent fever in rheumatic fever, rash and later more persistent joint changes, aspirin response dramatic in rheumatic fever.
2. *Acute osteomyelitis* – There may be no leucocytosis at the start and X-ray changes take two weeks or more to develop. With osteomyelitis of upper end of humerus, there may be pain on movements of both shoulder and elbow, thus simulating rheumatic fever acute arthritis. Child is likely to be more acutely ill.
3. *Henoch-Schonlein purpura* – may present with acute joint pains but often there is, in addition, relative painless swelling over the back of hands or of eyelids; there may also be bowel symptoms. More diagnostic is the maculopapular rash over buttocks and lower limbs, which turns haemorrhagic.
4. *Acute poliomyelitis* – Acute limb pain on movement for a day or two before paresis or obvious changes in reflexes develop.
5. *Acute leukaemia* – Acute pain and swelling of joints from periarticular inflammation, rarely haemarthrosis.
6. *Streptococcal tonsillitis* – followed by limb pain. The pain may be worse on movements of the limbs and maximal in relation to joints. The condition subsides rapidly with adequate treatment of throat infection.
7. *Sensitivity reaction* – to drugs, serum sensitivity and certain food allergies may cause migratory polyarthritis similar to rheumatic fever. Often associated with urticaria.
8. *Collagen diseases* – Polyarthritis can occur early in the course of polyarteritis nodosa, lupus erythematosus and dermatomyositis. The arthritic symptoms are usually mild and other characteristic features are either present or emerge as the patient is observed.

MANAGEMENT

1. ***Rest and nursing care*** – Rest in bed (Table 40). Speed of ambulation should be varied according to the severity and course of the rheumatic attack. In patients with polyarthritis without carditis, prolonged bed rest is not necessary. Patients with definite myocarditis and valvulitis should be kept in bed until: (i) the intensity of heart murmur has diminished or has become stabilized, (ii) heart sounds are of good quality, (iii) sleeping pulse rate is below 100 per minute, (iv) haematocrit is rising or normal and the CRP is negative and (v) there is a true weight gain. Convalescence may often take 6 months or longer.
2. ***Diet*** – Aim is to maintain nutrition. Only fluids if moderate or high fever. Vitamins and minerals.
3. ***Drugs*** – control acute exudative manifestations.
   (a) Antibacterial agents – Benzathine penicillin 1.2 million units IM followed by phenoxymethylpenicillin 500 mg b.d. for 10 days. If sensitive to penicillin Erythromycin 40–50 mg/kg for 10 days.

Table 40: General acceptable rules for bed rest

Status	*Rest*	*Ambulation*
No carditis	2 weeks	Gradual 2 weeks
Carditis, no cardiomegaly	4 weeks	4 weeks
Carditis with cardiomegaly	6 weeks	6 weeks
Carditis with CHF	Until criteria in text fulfilled	3 months

(b) Anti-inflammatory agents

- *Salicylates* – in the form of Aspirin 100 mg per kg body weight per day in 3–4 divided doses taken in milk or after meals. Continued for 2 weeks, then scaled down to 75 mg/kg for 4–6 weeks for both arthritis alone, and/or carditis with or without cardiomegaly. Signs of aspirin toxicity are – vomiting, tinnitus, and hyperpnoea. If these occur, the drug should be discontinued for one or two days and then restarted in a lower dose.
- *Steroids* – should be given with first signs of carditis. They suppress the activity and allow digitalis and diuretics to work, and if there is only potential failure, risk of development of failure is minimised. Rebound phenomena (reappearance of clinical or laboratory signs of rheumatic activity) may occur when steroid medication is stopped or the dosage reduced. Dosage – Prednisolone 2 mg/kg/day in divided doses for 2 weeks, gradually decreased over another 2 weeks. Aspirin should be started after 2 weeks of steroids and continued for 4 weeks beyond to prevent steroid rebound.

4. ***Symptomatic treatment*** – (i) Local treatment – Cradle to lift bed clothing from affected joints. (ii) Cardiac failure – Digitalis – 0.03–0.05 mg/kg total dose orally, 3/4 this dose if parenteral digitalisation necessary. Give 1/2 dose stat, 1/4 after 8 hours, 1/4 after another 8 hours. Daily maintenance 1/4th–1/5th total dose. Frusemide 2 mg/kg/day with oral pot. chloride, oxygen. (iii) Pain and restlessness – Codeine for chest pain and cough. (iv) Anaemia – Iron by mouth.
5. ***Convalescence*** – Physical activity not undertaken until clinical and laboratory evidence of rheumatic activity have been absent for at least 2 weeks after stopping of salicylates. Restriction of physical exertion is not necessary where there is satisfactory compensation, and moderate degree of physical activity is desirable, but exercise should be increased gradually.

PREVENTION AND PROPHYLAXIS

1. Immediate treatment of every suspected case of sore throat or streptococcal infection with penicillin or erythromycin for 10 days.
2. Change of environment and improvement of nutrition.
3. Antimicrobial prophylaxis – Oral phenoxymethylpenicillin 200,000 units twice daily, or benzathine penicillin G 1.2 million units IM once every 3 weeks. For patients sensitive to penicillin, Erythromycin 40 mg/kg/day can be used. Prophylaxis must be continued till the patient is 25 years old, or for 5 years from the last attack of rheumatic fever whichever is longer. Preferably life-long in patients with carditis as adults can get recurrences after many years. Must be used even in chorea.

RHEUMATIC CHOREA (SYDENHAM'S CHOREA, ST. VITUS' DANCE)

Aetiology: *Age* – maximum incidence at 10th year, rare after puberty. *Sex* – twice more common in girls. *Predisposing factors* – Mental strain, e.g. overwork at school, fright or shock, or pregnancy in young females. *Exciting cause* – Majority due to acute rheumatic fever. Rarely, diphtheria, encephalitis, chickenpox. Chorea is regarded as a diffuse meningo-encephalitis affecting the basal ganglia, cerebral cortex and pia arachnoid.

Clinical features: *Triad* – of emotional instability, hypotonia and semipurposeful movements.

Onset – Chorea may appear several weeks or months (usually more than 6 months) after an attack of acute rheumatic fever, or it may be the initial symptom of a rheumatic episode. The onset is usually gradual. The child becomes increasingly nervous, tends to drop things and stumbles frequently. Speech becomes indistinct and characteristic purposeless movements of arms and legs develop.

1. **Involuntary movements**
   - Face – constant bizarre grimacing.
   - Tongue – when protruded it may be impossible to hold it quietly (Jack-in-the-box or chameleon tongue) and its undulating jerky movements are described as those of a bag of worms. When asked to show the tongue, the child puts it out rapidly and may bite it to keep it out, or may jerk it back rapidly with reptilian speed. When talking, the tongue produces a clucking sound.
   - Ocular muscles may rarely participate in the involuntary movements.
   - Extremities – Movements appear first in hands, when arms are outstretched in front, the posture is one of flexion at the wrist and hyperextension at the metacarpophalangeal joints. Choreic hands or spooning of hands on shaking hand with the child, there is intermittent squeezing (milk-maid grip). If the upper limbs are held above the head, the palm faces outwards (pronator sign).
   - Lower extremities less affected. Gait may be clumsy.
   - Muscles of abdomen and neck may be involved.

- Respiration – alteration in rhythm. Breath is taken rapidly, held for some time, and let go with a sigh. Involuntary grunting noises common.
- Choreic movements are intensified by voluntary effort and excitement, and banished by sleep.

2. **Weakness of voluntary movements** – In mild cases, little or no impairment of power, but in severe cases the choreic movements may become less marked but the limbs progressively weaken.
3. **Associated movements** – incoordinated and exaggerated. The hand grip is characteristic, pressure is not steadily maintained but waxes and wanes as stated above. When patient clenches his fist, movements may occur in the face, trunk and limbs. When the hands are extended the wrist often flexes and the fingers hyperextended giving a so-called 'dinner fork' deformity.
4. **Psychiatric disturbances** – Emotional instability, meaningless laughing or crying; in severe cases, delirium. Eventually normalcy is regained.
5. **Muscular hypotonia** – It gives rise to characteristic dinner-fork deformity of the wrist and to pronation of the elevated hand.
6. **Reflexes** – Cutaneous reflexes often very brisk. Pendular knee jerk characteristic. If a chorea jerk coincides with testing the knee reflex, it will cause 'hung up' jerk. In severe cases deep reflexes may be absent. Ocular phenomena – pupils often dilated, hippus may be present.
7. **Speech** – Hesitating, distorted and monotonous, words spoken in a whisper or explosively. In severe cases, speech may be so severely affected as to be completely lost, and swallowing may be difficult.
8. **Rheumatic manifestations** – In 20–25% of cases, rheumatic heart disease develops. Pericarditis, arthritis and nodules are rarely associated with chorea and there is no fever.

Course – Chorea is a self-limited condition lasting on an average for 3 months, and usually there is complete recovery from the emotional and neuromuscular abnormalities. Recurrence occurs in about a third of patients and as many as five to six attacks may occur. It is unlikely 2 years after the first attack. Symptoms are less severe and duration shorter.

Varieties of Rheumatic Chorea

1. Hemichorea – movements confined to one side of body.
2. Paralytic chorea, limp chorea or chorea mollis – complete flaccidity of muscles and hypotonia. It is preceded by usual symptoms of chorea or rarely may be the first noticeable symptom.
3. Chorea gravidarum – rare but severe variety occurring chiefly in young women during earlier months of pregnancy. Chorea may recur with successive pregnancies.

Management

1. *General measures* – Bed rest indicated in most patients. If chorea is severe, change of environment may help and hospitalization is therefore better. Attention to fluids and nutrition of children unable to feed themselves.
2. *Sedatives* – Phenobarbitone 5 mg/kg/day. Alternatively chlorpromazine 2–3 mg/kg/day or haloperidol 0.2 mg/kg/day.
3. *Antistreptococcal treatment* – 10-day course of penicillin followed by prophylaxis.
4. *Suppressive drugs* – Salicylates or steroids may be indicated in patients with signs of an active rheumatic inflammatory process.
5. *Rheumatic penicillin prophylaxis.*

18. TUBERCULOUS MENINGITIS

AETIOLOGY

Age – highest incidence from 6 months to 3 years. Very rare before age of 3 months. *Sex* – equal incidence. Primary infection – usually in lungs or mediastinal glands, or bowel and mesenteric glands. Tubercle bacilli carried in the blood stream produce caseous foci called Rich's focus in brain, meninges, spinal cord. It is only when these rupture into the cerebrospinal fluid that meningitis results.

PATHOLOGY

Meningitic and encephalitic component.

Meninges – Rich's focus. Meningeal exudate at base of brain from optic chiasma anteriorly to mid-pons posteriorly. Exudate and later organizations and adhesions responsible for communicating and obstructive hydrocephalus, cranial nerve palsies, arterial compression and inflammation.

Brain – (a) Border zone encephalitis – Contiguous areas to meningeal inflammation show perivascular inflammation and softening. (b) Cerebral oedema and encephalopathy – Diffuse neuronal oedema due mainly to vascular damage and partly to hypersensitivity reaction to tuberculin. (c) Infarcts in distribution of arterial territories. (d) Ventricular dilatation – Hydrocephalus common to all cases. (e) Tuberculoma, mainly cerebellar, single or multiple. Can cause cerebellar signs, focal convulsions and raised ICT.

Blood vessels – Main arteries compressed or inflamed – middle cerebral, internal carotid or siphon, anterior cerebral. Rarely posterior cerebral and basilar.

CLINICAL FEATURES (CLASSICAL)

1. ***Prodromal stage of sensory irritability*** – (i) Onset insidious, rarely acute with high fever. (ii) Change in temperament – irritability, restlessness, disinclination to play combined with periods of drowsiness. (iii) Headache; older children may complain of it, younger children may indicate their pain by screams and by putting their hands to head. (iv) Anorexia and vomiting. (v) Constipation often severe. (vi) Temperature normal or only slightly raised. This stage lasts for a week or more.
2. ***Stage of meningeal irritation*** – (i) Convulsions. (ii) Evidence of meningeal irritation – child lies curled upon side, stiffness of neck, positive Kernig's and Brudzinski's signs. (iii) Tense anterior fontanelle and separation of cranial sutures. When anterior fontanelle is closed, separation of sutures gives rise to 'cracked-pot' resonance on tapping skull (Macewen's sign). (iv) Exaggeration of deep reflexes. (v) Grinding of teeth. (vi) Muscular twitchings. (vii) Squint usually internal, and ptosis. (viii) Temperature usually raised to 101-102°F, sometimes high throughout the illness. (ix) Disturbances of consciousness.
3. ***Terminal stage of coma*** – (i) Irritability – replaced by coma, child lies on back with eyes staring vacantly and dilated pupils. (ii) Rapid loss of weight and dehydration. (iii) Tachycardia and irregular pulse. (iv) Respiration irregular, often Cheyne-Stokes. (v) Tremors of limbs and occasionally choreic movements. (vi) Terminal hyperpyrexia. This stage also lasts approximately one week. (vii) Child may lie in position of decerebrate rigidity for many weeks. Stage 2 may be missed, stages 2 and 3 may be concomitant.

Fundoscopy – may reveal choroid tubercles especially when there is associated miliary tuberculosis. Papilloedema with raised ICT or optic nerve compression. Later secondary optic atrophy.

VARIATIONS

- Sudden onset, absent prodromal symptoms, and brief course.
- Initial manifestation may be hemiplegia or some other localising symptom, and meningeal symptoms occur later.
- Coma without meningeal manifestations.
- Temporary improvement or remission without treatment.
- Typhoid-like onset.
- Onset with status epilepticus.
- Tumour onset.
- Bronchopneumonic onset with respiratory symptoms.
- GI onset with vomiting, abdominal pain.
- With chronic head enlargement.
- Precipitation following head trauma.
- Hypersensitivity manifestations
  - Phlyctenular conjunctivitis
  - Erythema nodosum
  - Poncet's disease - Arthralgia and affections of large joints such as knees
  - Fever - High grade fever without definite evidence of progression of primary complex.

CSF – Clear or slightly opalescent. Pressure increased. Cells 50–500/cmm. mainly lymphocytes, initially polymorphs. Protein increased (above 50 mg per 100 mL). Sugar reduced (below 50 mg per 100 mL) in majority of early cases, a finding which excludes virus meningitis. The chloride content falls too late in the disease to be of much diagnostic importance. Direct examination of the fluid may reveal acid fast bacilli in centrifuged deposit or in the pellicle (cob-web) which forms when it is allowed to stand overnight. CSF may be normal or show Froin's syndrome if there is spinal subarachnoid block, rarely mimics pyogenic meningitis in the early stages. Newer serological techniques for acid fast bacilli, TB antibody by ELISA technique. Molecular DNA technology may help in near future for accurate diagnosis by identifying mycobacterial DNA by PCR (polymerase chain reaction) analysis.

CT Scan – will show cerebral oedema, basal exudates, areas of infarction and hydrocephalus.

See Table 41 for the complications and sequelae of TBM.

DIFFERENTIAL DIAGNOSIS

1. *Viral encephalitis See* Table 42.
2 *Other types of meningitis*: (Refer).

MANAGEMENT

I. GENERAL –
   1. Nursing–care of mouth and skin.
   2. Fluids – 1300-1400 mL/m^2, restricted to prevent cerebral oedema. Nasal feeds if child cannot take by mouth, chiefly milk and high-protein preparations.

Table 41: Complications and sequelae of TBM

• Cranial nerve palsies
• Tuberculous arteritis with infarction
• Hydrocephalus
• Meningoencephalitis
• Tuberculous serous meningitis
• Tubercular abscess
• Tubercular myeloradiculitis
• Endocrinopathies:
Hypothalamic syndrome with:
- Obesity or wasting
- Diabetes insipidus
- Precocious puberty
• Epilepsy

Table 43: Antitubercular RNTCP regimes

Tr. category	*Type of patient*	*Intensive phase*	*Continuing phase*
New	Sputum +ve Sputum –ve Extrapulmonary	2H3 R3Z3E3	4H3R3
Previously treated	Smear +ve relapse	2 I3 R3Z3E3S3	5 H3R3
	Smear +ve failure Smear +ve Treatment	IH2R3Z3E3	

Prefix indicates months of therapy and subscript indicates frequency of drugs to be given per week. Continuation phase in TBM is 7 months.

3. Multivitamin syrup
4. Indwelling catheter for retention of urine
5. Enema every 3rd or 4th day if constipation

Treatment under RNCTP is under two categories. New case and previously treated case. First line TB drugs. (Revised National Tuberculosis control program).

Note: In DOT an observer watches and supports the child in taking the drugs.

Steroids – by mouth may reduce inflammatory reaction and thereby decrease the incidence of spinal or ventricular block and release the tubercle bacilli from the fibrinous exudate so that they are more exposed to the action of drugs. It also produces rapid improvement in the general condition of the patient. Initial therapy with 0.5 mg/kg IV dexamethasone for increased intracranial tension, repeat at 0.2 mg/kg dose every 6–8 hours. Oral steroids: prednisolone 1–2 mg/kg/day for 4–8 weeks, followed by gradual discontinuation over 2–4 weeks.

Table 42: Differentiating features between viral encephalitis and tuberculous meningitis

Characteristic	*Viral encephalitis*	*Tuberculous meningitis*
Fluid	Clear	Clear, may have fibrin web on standing
Pressure	Normal or increased	Normal or increased.
Protein	Normal or increased	Increased. May be over 100 mg per cent.
Glucose	Rarely below 40 mg per cent. May be above 80 mg per cent. CSF/Blood ratio about 2/3.	Usually in region of 20–25 mg per cent. Rarely if ever above 45 mg per cent. CSF/Blood ratio <½.
Cells	May be normal. When increased usually of lymphocytes to 50–200/c.mm. Some polymorphs in first week.	Increased. In first few weeks polymorphs.
Organism	Isolated	M. tuberculosis may be seen on direct microscopy. Culture may be positive in 6–10 weeks
Antibodies	Antibody to particular virus may rise with serial samples.	Gamma globulin increased.

Table 44: Antitubercular drugs RNTCP regimes

Drugs	*Daily*	*Intermittent thrice weekly*	*Main adverse effects*
Isoniazid	5 mg/kg	12–17 mg/kg	Hepatotoxicity, Polyneuritis
Rifampicin	10 mg/kg	15 mg/kg	Hepatotoxicity, red-coloured body secretions
Pyrazinamide	25 mg/kg	35 mg/kg	Hepatotoxicity
Streptomycin	15 mg/kg	15 mg/kg	Vestibular damage
Ethambutol	15 mg/kg	30 mg/kg	Retrobulbar neuritis

CHEMOPROPHYLAXIS

Asymptomatic children under 6 years of age, exposed to an adult with infectious TB from within the same household are to be given 6 months of INH (10 mg/kg daily), irrespective of Mantoux's test and BCG vaccination status.

Patientwise Boxes (PWB)

These boxes have standardized drug therapy ready to use. For the purpose of treatment, paediatric population is divided into four weight based: 6–10 kg, 11–17 kg, 18–25 kg, and 26–30 kg. These boxes are given to the patients and supervised.

II. SYMPTOMATIC –

1. Convulsions – (i) Phenobarbitone 5–10 mg/kg IM stat, then 5 mg/kg once daily, or (ii) Diazepam 0.25–0.3 mg/kg slowly IV.
2. Irritability and increased tension – (i) Lumbar puncture. (ii) Mannitol IV 2.5–3 mL/kg one dose. (iii) Dexamethasone – mainstay of treatment for raised ICT. (iv) Acetazolamide 25–75 mg/kg daily for prevention of progressive hydrocephalus.
3. Fever – If above 39°C (102°F) antipyretics like paracetamol every 4 hours. Ice compresses to forehead and Eau de Cologne compresses to abdomen.
4. Constipation – Glycerine suppository or glycerine syringe.
5. Dehydration – 1/3 or 1/2 glucose saline.

III. SURGICAL – Insertion of ventriculoatrial or ventriculoperitoneal shunt in cases with severe hydrocephalus not responding to early medical treatment. Maybe lifesaving, but makes child shunt-dependent for life.

Complications – Infection, block, displacement.

19. INFANTILE CONVULSIONS

CAUSES

1. ***Febrile*** – Commonest type in childhood. Temperature of more than 38°C in absence of demonstrable CNS infection, e.g. upper respiratory tract infections, measles, pneumonia, pyelonephritis, otitis media. Seen between 6 months and 5 years.

   TYPES: *Simple typical* – is generalized clonic, lasts for less than 15 minutes, does not recur again within 30 minutes, recovers fully after 1/2–1 hour without neurological deficit. Drowsiness but no loss of consciousness following the seizure. Simple seizures may lead to epilepsy in 1% of children. *Complex or atypical seizure* – lasts longer than 15 minutes, may go into status, may be focal, may have residual neural deficit. Risk of epilepsy is about 10%.

   Febrile seizures can be familial.

2. ***Intracranial*** –
   - *Traumatic* – Birth injury, subdural haematoma.
   - *Vascular* – Cerebral arterial embolism or thrombosis, intracerebral haemorrhage, cortical thrombophlebitis, Sturge-Weber syndrome.
   - *Infection* – Encephalitis, meningitis, cerebral abscess, parasitic brain disease.
   - *Increased intracranial pressure* – Tumour, hydrocephalus, Reye's syndrome.
   - *Degeneration of brain* – Cerebrovascular degeneration, storage disorders.
   - *Malformations of brain.*
   - *Tumors of brain* – Astrocytoma, medulloblastoma, leukemic deposits.
3. ***Encephalopathies*** –
   - *Hypertensive* – Acute and chronic nephritis, congenital abnormalities of kidneys with renal rickets.
   - *Toxic* – Lead encephalopathy, convulsant drugs, e.g. camphor, phenothiazine, steroids; kernicterus.
   - *Allergic* – Vaccine sensitivity.
   - *Collagen disease* like SLE.
4. ***Epilepsy***.
5. ***Metabolic*** – Hypoglycemia, hypocalcemia, hypomagnesemia, alkalosis, hyponatremia. hypernatremia, pyridoxine deficiency and dependency, phenylketonuria and other inborn errors of metabolism.
6. ***Anoxia*** – Asphyxia neonatorum, breath holding spasms, whooping cough, Adam-Stokes syndrome, Fallot's tetralogy, suffocation, near-drowning, poisoning.
7. ***Tetanus.***

DIAGNOSIS AND INVESTIGATION

History:

1. AGE –

   Newborn – Intracranial birth injury, perinatal asphyxia, intracranial hemorrhage, tetanus neonatorum, tetany of newborn, hypoglycemia, kernicterus, sepsis and meningitis, inborn errors of metabolism, brain malformations, polycythemia.

   First 6 months – CNS infections, perinatal asphyxia, tetany, other metabolic defects.

   6 months to 3–4 years – Febrile convulsions, CNS infections, metabolic disorders, sequelae of perinatal asphyxia, early neurodegeneration, idiopathic epilepsy.

   3–10 years – Idiopathic epilepsy, febrile convulsions up to 5 years, residual cerebral damage from early trauma, infection, brain tumour, acute nephritis and certain degenerative diseases of the brain, lead poisoning.

2. RECURRENT OR NON-RECURRENT–

   Table 45 gives causes of convulsions.

3. BIRTH INJURY – History of previous convulsions and any difficulty experienced by mother or baby in the perinatal period.

Table 45: Causes of convulsions

Acute or nonrecurrent convulsions:
• Intracranial infections
• Intracranial haemorrhage
• Toxic
• Anoxic
• Metabolic disturbances
• Acute cerebral oedema
• Cerebral thrombosis
Chronic or recurrent convulsions:
• Febrile convulsions
• Epilepsy
• Hydrocephalus
• Tetany
• Hypoglycaemic states
• Uraemia
• Subdural hematoma
• Cardiovascular dysfunction
• Parasitic disease of brain
• Intracranial tumours
• Cerebral degeneration
• Migraine
• Lead poisoning

4. Family predisposition – in idiopathic epilepsy and in febrile convulsions.
5. Recent immunization procedures – Convulsions occasionally occur after vaccination against pertussis and very exceptionally may be evidence of post-vaccination encephalitis.
6. Head injury – Past history may suggest chronic subdural hematoma.
7. Poison ingestion or toxin exposure.
8. Relation to meals – Tendency for convulsions in early morning hours or at the end of a long interval between meals suggestive of hypoglycemia.
9. History of past encephalopathy – Children who have recovered from tuberculous meningitis or encephalitis may develop convulsions at a later date.
10. History of other systemic disease – such as cardiovascular, nephritis, bleeding disorder, collagen disease.

EXAMINATION

1. *Loss of consciousness* – absent in tetany, tetanus and rare in simple febrile seizures.
2. *Unilateral attacks* – Vascular thrombosis (commonest in TBM), brain tumour, cerebral abscess, focal encephalitis, tetany and lead poisoning.
3. *Fever* – Otitis media, pharyngitis, pneumonia, pyelonephritis, meningitis, sinus thrombosis. If clinical findings are negative and the child is less than 5 years of age, consider possibility of febrile convulsions.
4. *Blood pressure* – measurement to rule out hypertensive encephalopathy.
5. *Tautness or bulging of the fontanelle*, and rigidity or objection to flexion of neck.
6. *Stridulous breathing* – in an infant with rachitic bone changes should raise question of tetany.
7. *Pronounced asymmetry of face and/or cranium* – may provide outward evidence of cerebral agenesis, a facial naevus of intracranial haemangioma, superficial pigmented areas of neurofibromatosis, and facial adenomata with butterfly distribution of tuberous sclerosis.
8. *Localising signs* – in the central nervous system. Sixth nerve palsy (false) suggests raised intracranial pressure.
9. *Ophthalmological examination* – changes in discs in uraemia, cerebral tumour (not if infratentorial) and meningitis. Phakomas in tuberous sclerosis. Macular degeneration or cherry red spot in degenerative disorders.

INVESTIGATIONS

1. *Urine* – to exclude causal renal factor.
2. *CSF* – for diagnosis of meningitis, encephalitis.
3. *Imaging* – Radiograph – (i) Long bones – Lead line in lead poisoning. (ii) Skull – evidence of increased intracranial tension. (iii) Sutural separation. (iv) Angiography. (v) Brain scan. (vi) CT scan. (vii) MRI scan.
4. *EEG.*
5. *Blood chemistry.*

MANAGEMENT

A. ***Of an attack***

1. Loosen the child's clothes. Turn the child on one side and keep the airway patent. Prevent tongue biting by placing a mouth gag between the jaws, not made of metal.
2. Take temperature, if there is fever – (a) Tepid water compresses to head and body. (b) Eau de Cologne compresses to abdomen.
3. Anticonvulsants – (a) Diazepam or Lorazepam – 0.25–0.5 mg/kg very slowly IV without dilution. Danger of respiratory depression if bolus is given.

Repeated every 20 minutes if necessary. Action within 30 seconds. 1 mg/kg can be given rectally in an emergency. Treatment of choice. (b) Dilantin sodium – 10 mg/kg IV stat, then 5–8 mg/kg/day in two divided doses orally. Diazepam followed by IV bolus of Dilantin will control 90% of acute seizures. (c) Phenobarbitone sodium – 8–10 mg/kg IM stat, then 5 mg/kg in divided doses 12–hourly IM for 2–3 days for adequate blood levels, then 5 mg/kg orally once daily. (d) Intranasal Midazolam 0.2 mg/kg or IM is safe and equally effective.

4. CSF – to rule out meningitis.
5. Sodium bicarbonate for acidosis, oxygen and suction.

B. ***Treatment of special types of convulsions***

1. *Febrile convulsions* – (a) Paracetamol at start of fever. 10–15 mg/kg/every 4 hours. (b) Tepid sponging or ice cap. (c) Rectal diazepam at start of fever in dose of 1 mg/kg useful in simple febrile convulsions. No prolonged prophylaxis necessary.
2. *Atypical febrile convulsions* – Family history of epilepsy or neurologically abnormal child needs prophylaxis with phenobarbitone 3–5 mg/kg/day once at night, or valproate 15–20 mg/kg/day in 2–3 divided doses up to 5 years of age.
3. *Acute infection* – Antibiotic and antipyretic therapy.
4. *Tetany* – 2 mL/kg 10% calcium gluconate IV Oral maintenance 50-100 mg/kg elemental calcium (Calcium lactate has 13% elemental calcium).
5. *Hydrocephalus* – Repeated ventricular punctures or surgical procedures. Acetazolamide 50–75 mg/kg/day until surgery.
6. *Hypertensive encephalopathy* – Lumbar puncture to rule out intracranial infection. IV Mannitol 2.5–3 mg/kg 1–2 doses.
7. *Epilepsy*
8. *Seizures recurring without explanation especially seen after birth* – despite anticonvulsant therapy may be due to pyridoxine deficiency and respond to pyridoxine 50 mg IM or 50–100 mg by mouth.

20. SKULL

CHANGES IN HEALTH AND DISEASE

In health

1. Rate of increase in circumference of the head (*See* section on growth and development).
2. Anterior fontanelle normally closes at about 18 months. Most posterior fontanelles are closed at birth, or close by 3–6 months.

In disease

1. *Unduly large head or macrocephaly* – Hydrocephalus, subdural hematoma, intracranial tumour, rickets, achondroplasia, megalencephaly, gigantism, storage disorders.
2. *Microcephaly* – Cranium abnormally small in congenital microcephaly, chromosomal anomalies, craniostenosis, intrauterine infections, drugs and radiation, postnatal cerebral damage following birth asphyxia.
3. *Abnormal delay in closure of anterior fontanelle* – Rickets, hypothyroidism, hydrocephalus, osteogenesis imperfecta, cleidocranial dysostosis, malnutrition.
4. *Craniotabes* – Isolated areas of thinness and softness of the skull, especially the parietal areas, which indent with pressure of the fingers like a ping-pong ball. Causes – congenital, rickets, hydrocephalus, congenital syphilis, osteogenesis imperfecta.
5. *Hydrocephalus* – Globular shape, forehead bulges forwards and parietal bones bulge laterally above the ears. The anterior fontanelle may stretch from ear to ear and extend backwards to the posterior fontanelle. As the head enlarges, the child may have difficulty in holding it up. Associated with "sun-setting" of eyes.
6. *Skull of rickets* – Craniotabes commonest early sign. Central parts of frontal and parietal bones often harder and thicker, forming frontal and parietal prominences or bosses which give the skull a box-like appearance. If these prominences are separated by deep grooves, which correspond to the sutures of the skull bones, a "hot-cross bun" skull may develop.
7. *Anencephaly* – Osseous vault of cranium defective and brain underdeveloped.
8. *Craniostenosis* – Premature closure of sutures of skull resulting in deformities of head and frequently damage to the brain and eyes – (a) *Oxycephaly* – Premature closure of coronal sutures resulting in tower head, pointing in the region of anterior fontanelle. (b) *Scaphocephaly* – Skull narrowed in anteroposterior diameter but elongated in coronal diameter due to premature fusion of coronal suture. (c) *Dolichocephalic* – Anteroposterior elongation due to premature closure of sagittal suture. (d) *Mixed forms* of various syndromes.
9. *Hypertelorism* – Abnormally large distance between the eyes, and broadening of the roof of the nose due to overdevelopment of lesser wings of sphenoid bone.

10. *Lacunar skull* – Defects in the vault in the form of shallow depressions or deep cavitations extending to the outer surface and occurring mainly in the frontal or parietal areas. X-ray of skull shows irregular patches of rarefaction or lacunas. Often associated with meningocoele.

21. HYDROCEPHALUS

Hydrocephalus is an accumulation of fluid in the head. It is usually caused by disturbance of the flow or absorption of CSF. Table 46 lists causes of hydrocephalus.

TERMS USED IN HYDROCEPHALUS

Communicating hydrocephalus: Paraventricular enlargement with communication between the ventricles and subarachnoid space.

Non-communicating or obstructive hydrocephalus: Obstruction in the ventricular system or at the outlets of fourth ventricle.

Low, normal or intermittently raised pressure hydrocephalus: Chronic hydrocephalus, either communicating or non-communicating, presenting with gait disturbance, slowing of mentation/dementia and urinary incontinence (Hakim's triad).

Arrested hydrocephalus: Apparently stable ventriculomegaly despite a non-functioning shunt and with no apparent neurological sequelae, but deterioration and even death may occur unpredictably.

External hydrocephalus: Self-limiting absorption deficiency of infancy and early childhood with raised pressure, enlarged subarachnoid space and insignificant enlargement of ventricles; the condition usually resolves within 1 year.

CLINICAL MANIFESTATIONS

1. *Infants with mild or severe head enlargement at birth* – who subsequently exhibit progressive hydrocephalus due to congenital malformation.
2. *Infants born with normal head circumference* – who develop abnormally rapid growth of the head; hydrocephalus develops 2 or 3 months later. Due to milder forms of congenital malformations, sequelae of meningitis and birth trauma, particularly intraventricular haemorrhage in the premature.
3. *Heterogenous group* – Infants in whom hydrocephalus has resulted from inflammation and haemorrhage, neoplasm, skull deformities, etc.

Table 46: Causes of hydrocephalus

1. Obstruction to CSF flow within the ventricles:
Congenital:
Aqueduct stenosis, forking or atresia
Dandy-Walker syndrome (atresia of foramina of Luschka and Magendie)
Hind-brain abnormalities, spina bifida
Vein of Galen aneurysm
Space-occupying lesions:
Acquired aqueduct stenosis
Colloid and arachnoid cysts
Thalamic glioma
Intraventricular tumours
Posterior fossa tumours
Tentorial herniation
Ventricular haemorrhage
Prematurity
A-V malformation
2. Defects of flow in subarachnoid space:
(leptomeningeal inflammation)
Infections:
Pyogenic
Tuberculous, fungal
Haemorrhage:
Subarachnoid haemorrhage
Trauma
Meningitis carcinomatosis
Foreign matter
3. Defects of absorption of CSF at the arachnoid granulations:
Congenital deficiency of arachnoid granulations (uncommon).

4. *Normal pressure hydrocephalus* – Skull large, ventricles dilated, pressure normal.

Signs

1. *Enlargement of head* – Speed of enlargement is generally proportional to the elevation of the intracranial pressure. In proportion to the rapid expansion of the head, the face remains small. The downward displacement of the orbital plate pushes the eyeballs portion of the sclera. This together with a marked divergent squint and paralysis of upward gaze gives a very characteristic facial expression ("setting-sun" sign).
2. *Separation of sutures* – and widening and fullness of the anterior fontanelle.

3. *Veins of scalp* – may become prominent as a result of increased drainage of the blood from intracranial structures through the emissary veins to the superficial circulation.
4. *Wasting* – is common with progression of the hydrocephalus.
5. *Cracked pot resonance* – on percussion of the skull.
6. *Physical and mental development* – lag behind and in advanced stages deterioration of the acquired functions takes place. In long lasting and severe hydrocephalus, weakness and spasticity of all extremities eventually occur. Blindness may occur in terminal stages. Corticospinal signs in lower limbs and ataxia may be early signs.
7. *Epileptic manifestations* – commonly occur in one or another stage of the disease.

INVESTIGATIONS

Imaging

1. *Radiography of skull* – seldom required. (a) Evidence of raised intracranial pressure – thinning of skull, separation of sutures, wide fontanelle. (b) Aqueduct stenosis, small size of the posterior fossa and marked expansion of the vault of the skull. (c) Dandy-Walker malformation may be recognised by unduly prominent occipital region and calcification may indicate tumour or toxoplasmosis.
2. *CT scan* – Ventricular enlargement is easily seen and its extent can be assessed, possible site of block, malformations and thinness of cerebral mantle can be judged.
3. *Transfontanelle ultrasonography* – is useful in neonates because it is non-invasive and repeatable.
4. *MRI* – is helpful in complex cases to define multiple congenital lesions and anatomy at the foramen magnum. Dynamic MRI can image the pattern of pulsatile CSF flow.

Intracranial pressure monitoring – Saline-filled catheter or catheter-tipped transducer is inserted into lateral ventricle, brain or subdural space records a pulsatile pressure of 0–10 mm relative to the foramen of Munro when patient is lying flat. As the ventricles enlarge, the mean arterial pressure rises and spontaneous periodic waves become more pronounced.

Quantitative assessment of CSF circulation – Infusion of mock CSF into the ventricles or lumbar sac combined with CSF pressure monitoring enables measurement of outflow resistance, CSF production rate and stiffness of the brain.

Cognitive testing – both before and after shunting is helpful. Cognitive decline is a useful index of true shunt dysfunction in a headache-prone child.

MANAGEMENT

1. *Treatment of cause* – Failing this obstruction to CSF outflow should be relieved. Patients requiring long-term CSF diversion can be treated with shunt or with endoscopic third ventriculostomy.
2. *Endoscopy* – In case of non-communicating hydrocephalus caused by obstruction distal to the third ventricle, an endoscope is inserted into the third ventricle, via a frontal burr hole. The thinned-out floor is visualized and a hole is made through this allowing CSF to drain into the basal cisterns.
3. *Drugs* – Acetazolamide 50–75 mg/kg/day decreases CSF production and in conjunction with corticosteroids or diuretics helps to control hydrocephalus in premature infants until they are well enough to undergo surgery.
4. *Hydrocephalus shunts* – CSF is usually drained from the ventricular system via a ventricular catheter (a valve with reservoir mechanism and distal catheter) into the peritoneal cavity. Lumboperitoneal shunts are used to drain fluid from lumbar subarachnoid space to the peritoneal cavity in some patients with communicating hydrocephalus. Complications–Shunt malfunction, shunt infection, overdrainage causing subdural hematoma, underdrainage, slit ventricles, multilobulated hydrocephaly, seizures, abdominal complications (peritoneal pseudocysts, bowel perforations, hernias).

In some cases of hydrocephalus complicating TB meningitis where insertion of shunt would result in shunt blockage caused by shunt infection, a temporary external ventricular drainage tube (EVD) is placed to drain the CSF for a few days.

22. CEREBRAL PALSY (LITTLE'S DISEASE)

Non-progressive central motor deficit due to prenatal or perinatal causes. Distinct from mental retardation.

CAUSES

1. Perinatal asphyxia (hypoxic-ischemic encephalopathy). 2. Birth injury. 3. Congenital malformations of the brain. 4. Kernicterus. 5. Inborn errors of metabolism. 6. Prenatal infective or vascular insults.

CLINICAL PICTURE

Clinical types:

1. *Spastic CP* – Quadriplegia, hemiplegia, paraplegia or monoplegia. Hyper-excitability, persistence of neonatal reflexes (such as exaggerated Moro's reflex or persistent asymmetric tonic neck reflex), arching of the back, scissoring of the legs, brisk deep jerks, swallowing difficulties and drooling of saliva.
2. *Extrapyramidal CP* – Choreoathetosis or dystonia. Hypotonia in early life, choreoathetosis in later life. Choreoathetosis with weakness seen with kernicterus.
3. *Atonic CP* – (a) Atonic diplegia, characterised by hypotonia, severe mental retardation and brisk tendon reflexes or rarely (b) congenital cerebellar ataxia. Cerebellar signs develop by second year of life. Mental retardation mild.

PREVENTION

Good antenatal and perinatal care. Proper management of premature and jaundiced babies.

MANAGEMENT

Team approach by paediatrician, neurologist, psychologist, physiotherapist, occupation therapist, orthopaedic surgeon, and speech therapist. Positive prenatal approach is helpful. Prognosis will depend upon the extent of brain damage and facilities available. Injection of Botulinum toxin to reduce spasticity. Surgery in carefully selected cases to reduce spasticity.

23. BREATH-HOLDING SPELLS

A conduct disorder in children from age of 6 months to 5 years.

TYPES

Cyanotic - Precipitated by anger or frustration. After a bout of crying, most of the air in the lungs is exhaled but there is no inspiratory effort and the vocal cords which were narrowed during crying, close. Breath is held for a few seconds in expiration and the child turns blue. If hypoxia continues, there is rigidity and opisthotonus, the child may lose consciousness and convulsions may occur. Child recovers consciousness but becomes limp for some time. In some cases if the child is given a painful stimulus it will take another breath and begin a fresh bout of crying and the impending attack may be aborted.

An attack could be aborted by a strong physical stimulus such as a pinch at the onset of the spell. Reassurance to parents about benign nature of the episodes. Purposeful neglect of the child after it recovers.

Acyanotic or *pallid* are not true breath holding spells but a type of brief reflex asystole following unexpected painful stimulus. Child may become rigid and may develop clonic seizures. Attempts to abort an attack by painful stimulus are contraindicated.

24. CHILDHOOD ENURESIS

Bed-wetting by children beyond the age when control of urinary bladder should have been acquired, due to delay in the maturing of physiological reflex bladder control.

Aetiology – More common in boys, first born children, children who have experienced stress in early life, lower social classes.

TYPES

- *Intermittent* – Only occasional dry night.
- *Primary or true* – Child has never had a single dry night (rare over age of 5 years).
- *Secondary or acquired* – Enuresis develops at the age of 5 in a child who has been previously dry at night for at least 12 months.

CAUSES

- *Genetic factors* – A boy with intermittent nocturnal enuresis has 75% chance of having a first degree relative who also wets the bed after age of 5 years.
- *Delay in establishment of bladder control* – due to maturational delay, chronic illness, improper or inadequate training, or small functional bladder capacity.
- *As a symptom of organic illness* –
  - (a) Neurological – Epilepsy, spina bifida, cerebral palsy, nutritional deficiency.
  - (b) Endocrine – Polyuria in diabetes mellitus, diabetes insipidus.
  - (c) Urinary – Pyelonephritis, TB, congenital malformations, calculi, chronic nephritis, ectopic ureter.
  - (d) Genitalia – Balanitis, meatal ulcer, vulvo vaginitis, threadworms.
  - (e) Post-operative anxiety, trauma- induced.
- *As a symptom of psychological ill-health* and without evidence of organic disease.

INVESTIGATIONS

- *Urine* – for glucose, albumin and blood. Microscopy and culture to exclude UTI.
- *Ultrasound or other radiological investigation* – if urinary tract infection or history suggesting anatomical abnormality of urinary tract (e.g. straining on micturition or persistent dribbling of urine).

MANAGEMENT

1. Confidence and training – Aim is to treat the bed-wetter not the bed-wetting. Scolding and punishment should be avoided. Child should empty bladder before going to bed. For some time child may be awakened 2–3 hours after sleep and made to evacuate bladder, and again in the early morning. Restriction of fluid in latter part of day. Bladder capacity training in daytime by holding of urine for progressive increase of time before voiding.
2. Correction of physical defects and improvement of general health.
3. Condition therapy –
   (a) *Dry bed training* – requires skilled therapist and maximum compliance by the family.
   (b) *Enuresis alarms* – depend on the completion of an electrical circuit when urine is passed and then an alarm goes off. The child then has to get out of bed, switch off the alarm, and go to the toilet before setting up the system again.
   Types of alarms – (i) Pad and bell – The sensor pad is a plastic mat imprinted with electric current. (ii) Body-worn alarm – A tiny electrical sensor is attached to the child's thigh or pants and is connected to a minialarm worn on the shoulder or in the pocket of the pyjama jacket.
4. Drugs – can be used when conditioning therapy is inappropriate, or to achieve dryness quickly, e.g. temporary period during a school trip or holiday.
   (a) *Antidiuretics* – Desmopressin – given as metered-dose aerosol intranasally, starting with 20 mg last thing at night and increasing to maximum of 40 mg.
   (b) *Oxybutynin* – 2.5 mg at bed time.
   (c) *Tricyclic antidepressants* – Imipramine 25 mg at night increased to 50 mg or 75 mg depending on size of the child.

25. DOWN'S SYNDROME (MONGOLISM)

AETIOLOGY

Chromosomal abnormality. Majority born to elderly mothers, have trisomy 21 due to nondisjunction at meiosis due to ageing of the oocyte. A small percentage born to young mothers, have translocation of the chromosomes in the D group with 21.

CLINICAL FEATURES

1. *Mental retardation* – of moderate to severe degree. Pleasant temperament. 2. *Skull* – small, brachycephalic. Excessive skinfolds at back of neck. 3. *Eyes* – Orbits small, mongoloid slant of the eyes. Epicanthic folds. Blepharitis, strabismus, speckling of the iris (Brushfield spots). 4. *Ears* – Small low set. May be deformed. 5. *Tongue* – protruded, fissured (scrotal tongue). 6. *Nose* – short with flattened bridge. 7. *Teeth* – Delayed eruption, protruded lower jaw. 8. *Generalized hypotonia* – causing protuberant abdomen, diastasis recti, and umbilical hernia. 9. *Extremities and phalanges* – short, hands and feet appear broad and square. Fifth finger is short and tends to be incurved due to atretic second phalanx. Wide space between first and second fingers and toes (sandal gap). Single transverse palmar crease. 10. *Bony pelvis* – Broad ilia, smaller acetabular angles and elongated ischia. 11. *Congenital cardiac defects* – most commonly endocardial cushion defects, ASD or VSD. 12. *Genitalia* – poorly developed. 13. *Prone to skin and respiratory infections*. 14. *Others* – Incidence of leukaemia, GI malformations such as duodenal atresia and Hirschsprung's disease, and hypothyroidism higher as compared to general population.

DIAGNOSIS

Diagnosis by karyotyping (trisomy 21). Young mothers also have to be karyotyped to rule out translocation. In nondisjunction recurrence risk in most children less than 1%, with translocation can vary from 10 to 15%.

MANAGEMENT

1. Multidisciplinary approach to mental handicap. 2. No drugs effective. 3. Genetic counselling. 4. Prenatal diagnosis by USG, chorion villus biopsy or amniocentesis. Maternal serum alpha-fetoprotein is lowered considerably if

Table 47: IAP immunization time table 2011

Age (completed weeks/months/years)	*Vaccines*
Birth	BCG OPVO HepB 1
6 weeks	DTwP1/DTaP1 OPV1*/OPV1 + IPV1 Hib1 HepB2 Rotavirus 1*# PCV 1
10 weeks	DTwP2/DTaP2 OPV2*/OPV2 + IPV2 Hib2 Rotavirus 2 PCV2
14 weeks	DTwP3/DTaP3 OPV3*/OPV3 + IPV3 Hib3 Rotavirus 3 HepB3** PCV3
9 months	Measles
12 months	Hepatitis A 1
15 months	MMR1 Varicella PCV Booster
16 to 18 months	DTwP B1/DTaP B1 OPV4*/OPV4 + IPVB1 Hib B1
18 months	Hepatitis A2
2 years	Typhoid 1#
5 years	DTwP B2/DTaP B2 OPV5 MMR2$ Typhoid 2 Varicella 2$$
10 to 12 years	Tdap/Td & HPV^

*OPV alone if IPV cannot be given
*# Rotavirus vaccine (2/3 doses (depending on the brand) at 4–8 weeks' interval)
** The third dose of Hepatitis B can be given at 6 months
$ The second dose of MMR vaccine can be given at any time 4–8 weeks after the first dose
$$ Varicella (2nd dose may be given any time 3 months after the 1st dose)
Typhoid revaccination every 3 years
& Tdap preferred to Td, followed by repeat Td every 10 years
^ Only females, three doses at 0, 1-2 and 6 months

foetus has Down's syndrome, indication for prenatal testing. Maternal infections known to damage the foetus are – Rubella, cytomegalovirus, HIV, toxoplasmosis, varicella zoster, human parvovirus, herpes simplex, Treponema pallidum.

Table 48: IAP recommended vaccines for adolescents (10 years to 18 years)

Vaccine	*Schedule*
TdapfTd&	10 years
HPV^	10 to 12 years

&Tdap preferred to Td, followed by repeat Td every 10 years (Tdap to be used once only)
^ Only females, three doses at 0, 1 or 2 (depending on the vaccine used) and 6 months

Table 49: IAP Recommendations for catch up Immunization in adolescents

Vaccine	*Schedule*
MMR	2 doses at 4–8 weeks interval@
Hepatitis B	3 doses at 0, 1 and 6 months#
Hepatitis A	2 doses at 0, 6 months (prior check for Anti HAV IgG may be cost effective)##
Typhoid	1 dose every 3 years**
Varicella	2 doses at 4–8 weeks interval

@ one dose if previously vaccinated with one dose
#.## Combination of Hep B and Hep A may be used in 0, 1, 6 schedule
** A minimum interval of 3 years should be observed between 2 doses of typhoid vaccine

Table 50: IAP Recommendations for adolescent Immunization in special circumstances

Vaccine	*Age recommended*
Influenza vaccine	One dose every year
Japanese encephalitis	Vaccine Catch up to 15 years@
PPSV23 (Pneumococcal) vaccine	2 doses 5 years apart*
Rabies vaccine 0, 3, 7, 14, 28 day	As soon as possible after exposure

@Only in endemic area as catch up;
* Maximum number of doses–Two

26. IMMUNIZATION IN CHILDREN

IMMUNIZATION OF ADOLESCENTS

Adolescence should be considered an appropriate age for catch up immunization as well as for administration of certain vaccines which may not have been available earlier. Preferred age for administration is at 10–12 years but catch up may be done till 18 years. Vaccines to be considered for adolescents if not received earlier include.

PRECAUTIONS AND CONTRAINDICATIONS TO IMMUNIZATION

(a) Antigens should not be given in the presence of severe respiratory or other infections, can be given in presence of minor respiratory or GI infection. (b) Antigens should

Table 51: IAPCPI recommendations for immunization of HIV infected children

Vaccine	*Asymptomatic*	*Symptomatic*
BCG	Yes (at birth)	No
DTwP/DTaP/TT/Td/Tdap	Yes as per routine schedule at 6w, 10w, 14w, 18m and 5 years	
Polio vaccines	IPV at 6, 10, 14 weeks, 15–18 months and 5 years If indicated IPV to household contacts If IPV is not affordable, OPV should be given*	
Measles vaccines	Yes, at 9 months	Yes if CD4 count ≥ 15%
MMR vaccine	Yes, at 15 m and at 5 y	Yes if CD4 count ≥ 15%
Hepatitis B	Yes, at 0, 1 and 6 months	Yes, four doses, double dose, check for seroconversion, regular boosters Hib Yes as per routine schedule at 6w, 10w, 14w and 18m
Pneumococcal vaccines	Yes as per routine schedule at 6w, 10w, (PCV and PPV 23) 14 w and 15 m	
Inactivated Influenza	Yes as per routine schedule beginning vaccine at 6m, revaccination every year	
Rotavirus vaccine	Insufficient data to recommend	
Hepatitis A vaccine	Yes	Yes, check for seroconversion, boosters if needed
Varicella vaccine	Yes, two doses at 4–12 weeks' interval	Yes, if CD4 count ≥ 15% two doses at 4-12 weeks' interval
Vi typhoid vaccine	Yes as per routine schedule at 2 y and every 3 years	
HPV vaccine	Yes (females only) as per routine schedule 3 doses at 0, 1–2 and 6 m and at 10 years	

* OPV has been found to be generally safe in HIV infected especially in early stages.

be injected deep subcutaneously or intramuscularly. (c) A history of frequent repeated convulsions with possibility of epilepsy would contraindicate giving of pertussis vaccine in combined prophylaxis, or the child should be given phenobarb 6 mg/kg for 2 days prior and 2 days after giving the vaccine. (d) History of personal or family allergy exemplified by infantile eczema is not a contra-indication unless the first dose of combined vaccine produced an exacerbation. In such an instance, it is advisable to give the antigens separately; if a further reaction occurs after a particular antigen, its use should be discontinued. (e) Vaccination should not be done in the presence of eczema or skin infection, and the site of vaccination should be covered lightly, if at all.

BCG VACCINATION

BCG vaccine is made from a live attenuated strain of bovine tuberculosis bacilli. A preliminary Mantoux or other tuberculin test should be done to eliminate positive reactors for whom vaccine is contraindicated.

Indications:

1. Tuberculin negative persons at any age. It is quite safe to vaccinate newly-born babies. They react with as high a percentage of positive results as adults.
2. Non-reactors in homes where there are tuberculous patients.
3. Persons constantly exposed to infection such as medical students, nurses, hospital and sanatoria personnel.
4. All Mantoux-negative young adults.

Method – Intradermal injection of 0.1 mL of freeze-dried BCG vaccine with disposable or heat-sterilised syringe and needle or dermojet usually into the skin over the left deltoid. About a week after the injection, the local reaction starts as a small red papule which develops into a vesicle and breaks down into a small sore over the next few weeks. Use of the vaccine causes long-lasting or permanent conversion of the tuberculin reaction from negative to positive in almost all cases.

Ill-effects – rare. 1. Occurrence of abnormally large sore or local abscess which can be treated by antibiotics. Disseminated tuberculosis (very rare) often in infants and children with pre-existing immunological defects. 2. Large axillary lymphadenopathy. Can be excised, given a trial with 10 days of Erythromycin; if still enlarging antituberculous treatment.

OTHER VACCINES

Cholera

Oral cholera vaccines – Efficient method of eliciting intestinal mucosal immune response.

1. Killed VC vaccine with CTB subunit
2. Killed VC vaccine without CTB (subunit)
3. Reformulated killed VC vaccine without CTB subunit (Shanchol) contains both 01 and 0139 serotypes.

It is administered as two-dose regimen and does not require an oral buffer. It also gives herd protection.

Rotavirus Vaccine

Rotavirus is a major cause of diarrhoea related morbidity and mortality in children. Rates are similar in both the developed and developing world and in children of all socio-economic status.

Generally two live oral vaccines are licensed and marketed worldwide.

1. Human monovalent live vaccine derived from human Rotavirus strain 89.12 grown in vero cells and contain G1P1 (8) strain administered orally in 2 dose scheduled to infants of approximately 2–6 months of age.
2. Human Bovine pentavalent live vaccine is a Human Bovine reassortant vaccine and consists of five reassortants between the bovine WC3 strain and human G1, G2, G3, G4 and PIA (8) rotavirus strains grown in vero cells and administered orally in a three dose schedule at 2, 4 and 6 months. Both vaccines have shown excellent protective efficacy against rotavirus gastroenteritis.

HPV Vaccine for Protection against Cervical Cancer

There are 2 types of vaccines

1. Bivalent vaccine is a mixture of L1 proteins of HPV serotypes 16 and 18
2. Quadrivalent vaccine is a mixture of L1 proteins of HPV serotypes 16, 18, 6 and 11

Both are equally safe. Should be stored at 2 to 8°C

Dose is 0.5 ml intramuscular in deltoid

Bivalent vaccine is given 0, 1 and 6 months

Quadrivalent vaccine is given 0, 2 and 6 months

Vaccine is advocated from 10 years to 45 years in all females.

ADDENDUM

Pointers to Organic Cause

- Pain – (a) Localized in non-paraumbilical region. (b) Referred pain. (c) Sudden onset of severe pain. (d) Pain awakens child from sleep.
- High fever
- Dysuria
- Jaundice
- Anorexia/weight loss
- Abnormal physical findings
- Reduced activity of the child

Table 52: Acute abdominal pain in children

Medical	*Surgical*
Child < 2 years	
• Gastroenteritis	• Volvulus
• Lower lobe pneumonia	• Malrotation
• Acute pyelonephritis	• Intussusception
• Hepatitis	• Incarcerated inguinal hernia
• Subacute bacterial peritonitis	• Appendicitis
• Mesenteric adenitis	• Necrotizing enterocolitis
Child > 2 years	
• Acute non-specific pain	• Appendicitis
• Gallstones	• Intestinal obstruction
• Inflammatory bowel disease	• Meckle's diverticulitis
• Pancreatitis	• Peritonitis
• Urinary tract infection	• Cholecystitis
• Mesenteric lymphadenitis	• Incarcerated inguinal
• Henoch-Schonlein purpura	• Hernia
• Lead-poisoning	• Trauma-induced
• Primary peritonitis	• Splenic rupture/hematoma
Chronic or recurrent	
< 2 years	**> 2 years**
• Colic	• Functional (non-organic)
• Malabsorption	• Giardiasis
• Milk allergy	• Constipation
• Rotational defects	• Intra-abdominal abscess
• Hirschsprung's disease	• Lead-poisoning
• Oesophagitis	• Abdominal migraine/epilepsy
	• Urolithiasis

Investigations

History

- Pain – Time of onset, location, radiation, character
- Other symptoms – Anorexia, nausea, vomiting, diarrhoea
- Systemic symptoms
- Family history

Table 53: Normal average BP

Age	*Systolic*	*Diastolic*
1–3 months	75 ± 5	50 ± 5
4–12 months	84 ± 5	65 ± 5
1–8 years	95 ± 5	65 ± 5
9–14 years	100 ± 5	65 ± 5

Examination

- General: Activity of child, ill appearance, lethargy, rolling in bed in discomfort.
- Abdomen: Diastasis, tenderness, organomegaly, abdominal mass, bowel sounds (paralytic ileus), hernial sites.
- Systemic examination

Normal BP in Children

Differentiation between breath holding spells and epileptic seizures

Breath-holding spells	*Seizures*
Precipitating factors	Usually no ppt. factors in such as anger or fright
Blue at beginning	Blue at late stage
Crying precedes episode	No crying before seizures
No tonic/clonic phase	Tonic/clonic phase of convulsions
Duration 1 min.	Can last for any duration

Causes of chronic cough

- Bronchial asthma
- Recurrent normal infections
- Prolonged infection
- Aspiration
- Habitual cough
- Cigarette smoke (passive action)
- Intrabronchial foreign body
- Suppurative lung disease
- Congenital abnormalities

Serous meningitis

A few children with suspected TB meningitis and CSF pleocytosis recover without any treatment, an early meningitis undergoing natural cure is an immune competent child.

Characteristics of diarrhoea caused by rotavirus

1. Indistinguishable clinically from other causes of infantile diarrhoea.
2. Short incubation period (2–3 days).
3. Abrupt onset – Vomiting often precedes diarrhoea.
4. Illness usually lasts about one week, but usually improves within 2–3 days.
5. Temporary neutropenia may occur.
6. The illness may be very severe.
7. Hospital-acquired infection is common.

Maternal infections known to damage the foetus

Rubella	Varicella zoster
Cytomegalovirus	Human parvovirus
Toxoplasmosis	Treponema pallidum
HIV	Herpes simplex

Foetal nuchal translucency

In the foetus, fluid collecting behind the neck can be detected as nuchal translucency by ultrasound scanning, and it can be measured. The more the fluid has accumulated, the greater the risk of an abnormality being present. Chromosomal abnormalities, e.g. Down's syndrome can cause fluid accumulation.

VACTERL association

It is an association of birth defects:

- Vertebral anomalies
- Anal atresia
- Cardiac defect, most often ASD
- Tracheoesophageal fistula
- Renal (kidney) abnormalities
- Limb abnormalities (most often radial aplasia)

CHAPTER

13

Psychiatry

1. INTRODUCTION

Psychiatry, also known as Psychological Medicine, is that branch of medicine which deals with the diagnosis, treatment and prevention of mental disorders.

Psychology is the science which studies the structure and functions of the mind.

Mind: According to psychoanalytic theory, the human mind consists of two parts: (a) The Conscious or the strata of mind within one's awareness; which forms only a small portion. (b) The Preconscious or the strata of mind between the conscious and the unconscious that serves as a boundary or water-shed between the two helps to mediate information between these two parts.

Psychoanalytic theory postulates that an individual's mind comprises of three components, namely – (a) Id – contains instinctual and repressed impulses and is unconscious. (b) Ego – The reality based part the mind that regulates and channelizes instinctual desires and impulses; this component is partly conscious and partly unconscious. (c) Superego – decider of which instinctual impulse to be permitted an outlet, "rewarding and punishing" aspect of self, produces guilt when disobeyed. This component is partly conscious and partly unconscious.

Personality: *Definition:* Unique characteristics of an individual which differentiate one person from another. Depending on the dominant personality traits various kinds of personalities can be described.

1. *Aggressive* – dominating and assertive.
2. *Anxious* – worrying over trivial and minor things, highly strung, irritable and panicky.
3. *Hypomanic* – always happy and cheerful, happy-go-lucky type, witty and jovial, extroverted.
4. *Histrionic* – exhibitionistic and dramatizing, attention seeking, immature, highly suggestible.
5. *Avoidant* – shunning responsibilities, diffident.
6. *Melancholic* – depressed and sad, pessimistic outlook and philosophy.
7. *Obsessive* – rigid in habits and outlook, perfectionist, conscientious, fond of cleanliness, regularity and punctuality.
8. *Paranoid* – extremely suspicious.
9. *Psychopathic or antisocial* – antisocial traits like lying, stealing, etc., nonconformist; not observing the codes of ethics, culture, etc.; very little feelings of shame and guilt, cannot evolve stable emotional relationship.
10. *Schizoid* – shy, reserved, asocial, poor mixers, have very few friends, introverted.
11. *Dependant* – Unduly compliant to wishes of others, fears abandonment, allowing others to make decisions for self.

Knowledge of individual's personality helps in – (a) Understanding behaviour of normal persons. (b) Diagnosing the patient's psychological problems. (c) Predicting the response to treatment. (d) Rehabilitating the patient after recovery from illness.

Causes of mental disorders: The development of psychiatric disorders depends upon an interaction between predisposing and precipitating factors.

Predisposing factors: These determine an individual's vulnerability to develop psychiatric disorders. Many of these operate from early life. Some of the predisposing factors are: (a) *Biological factors* – heredity, constitution, metabolic and biochemical abnormalities, physical defects and illnesses.

(b) *Psycho-social factors* – personality traits, faulty parent-child relationships, psychologically traumatic experiences during early years, socioeconomic conditions, adverse life events.

Precipitating factors: These are events that occur before the onset of a psychiatric disorder and appear to have induced its onset. These could be: (i) *Physical* – Puberty, pregnancy, childbirth, menopause, systemic disease, drugs, etc. (ii) *Psychological* – Disturbed interpersonal relationships, marital disharmony, financial difficulties, occupational maladjustments, etc. (iii) *Environmental* – Calamities: War, famine, earthquakes, cyclones, etc.

(iv) *Sociocultural factors* – Sexual discrimination, racial discrimination, migration, etc.

Dynamics of mental illnesses – The predisposing factors determine an individual's susceptibility to mental illness. Individuals who are less susceptible can bear a greater severity of stress. Their capacity to handle tension (i.e. the emotional counterpart of unresolved conflicts or dilemmas) is high and their threshold to tolerate stress is high. Individuals who have a low threshold to tolerate stress are more susceptible to the development of mental disorders. Any stress – Physical, physiological and/ or psychological – acting as "the last straw on the camel's back", exacerbates this tension and can result in the onset of a psychiatric disorder which may manifest as disturbances in physiological, psychological and/or social functioning.

2. DIAGNOSIS AND INVESTIGATION OF A PSYCHIATRIC PATIENT

The diagnosis of a mental disorder is arrived at by carrying out the following:

1. History:
   a. Chief complaints with their origin, duration and progress.
   b. Associated symptoms related to physical or psychological dysfunction (disturbances in sleep, appetite, bowel functions, etc.).
   c. Past history of similar illness or any other mental and/or major physical illness.
   d. Family history of mental disorders.
   e. Personal history – regarding information about stressful situations during childhood, adolescence, school and college life; occupational, social, marital and psychological difficulties.
   f. Clinical assessment of dominant personality traits. (Premorbid personality)
2. Psychiatric examination – to detect disturbances in thinking, emotion, behavior, orientation, perception, memory, intelligence, insight and judgment.
3. Physical examination.
4. Investigations –
   a. *Laboratory investigations* – Blood, urine, stool examination, radiological studies, ECG, liver and kidney function tests, etc. to rule out physical disorders.
   b. *Brain imaging* – CT, MRI scan, SPECT, MR angiography. EEG, Brain Electrical Activity mapping (BEAM), PET.
   c. *Special investigations* –
      - *Social or environmental investigations* done by the Psychiatric Social Worker through interviews with the patient, relatives, friends and employers, held either in the hospital or by paying a visit to the home or the place of work. The aim is to study the milieu or the environment in which the patient has lived before becoming sick. An attempt is made to understand the role of various factors like cultural and religious background, family and social relationship, childhood experiences, school and college life, occupational adjustments, financial problems, marital and sexual difficulties, etc. in the development of the individual's personality and his illness.
      - *Psychological investigations* done by the clinical psychologist with the help of standardised tests.

TYPES OF PSYCHOLOGICAL TESTS

1. *Intelligence tests* – (Verbal and performance tests) to assess intelligence. The commonly used tests are Kamat-Binet test, Bhatia's test, Goddard form board, Raven's progressive matrices, Wechsler's Intelligence Tests for adults and children.
2. *Personality tests* – to assess the pre-sickness personality traits, the psychological conflicts and the nature of personality disturbance. Commonly used tests are Rorschach test, Thematic Apperception test, Minnesota Multiphasic Personality Inventory and Eysenck Personality Inventory.
3. *Aptitude tests* – to find out the natural likes and dislikes of the patient and his proficiency in any particular field. This information helps in vocational and educational guidance and rehabilitation of the patient, e.g. DAT (Differential Aptitude Test).
4. *Neuropsychological tests* – to assess an individual's higher mental functions. Tests used for this purpose include Wechsler's Memory Scale, Bender-Gestalt visual motor co-ordination test, etc.
   - Observations by an Occupational Therapist are sometimes necessary to get an objective evaluation of the (a) patient's mental state, particularly behaviour, and (b) progress in the recovery of the patient undergoing treatment.
   - Observations by a psychiatric nurse on the patient's ward behaviour.

Rating scales – to quantify the psychopathology observed, e.g. Brief Psychiatric Rating Scale (BPRS), Scale for assessment of negative symptoms (SANS), Scale for assessment of positive symptoms (SAPS), Hamilton Depression Rating Scale (HDRS).

3. DELIRIUM, DEMENTIA, AMNESTIC AND OTHER COGNITIVE DISORDERS

DELIRIUM

Delirium is a transient condition of disordered consciousness with global impairment of cognitive function. It a syndrome and not a disease with most of its causes lying outside the CNS. It is seen in 10–30% of patients in medical settings and may be seen more in intensive care cases.

Clinical Features

Delirium may develop acutely or subacutely, and normally lasts less than 7 days. It is characterized by a fluctuating level of consciousness ranging from extreme drowsiness to intense arousal, with motor restlessness, disorientation and disorders of perception. Patients are often frightened and irritable, with disturbed thinking and memory, as well as illusions; they may also experience vivid visual and, less often, auditory hallucinations. There is normally associated diffuse slowing of EEG, except in delirium tremens when increased fast activity may be observed.

Causes

Causes of delirium are listed in Table 1.

Management

a. Diagnosis and treatment of the cause. Sometimes the cause of delirium is known when the patient presents (e.g. withdrawal from alcohol, or with rapidly deteriorating hepatic function). However if there is no known cause, since the patient's ability to give an accurate history is limited, an account from someone who knows the patient should include inquiries about presence of any known illness, use of any prescribed or illicit drugs and an account of the events at the time the current symptoms developed. Physical examination and investigation must be guided by the knowledge that delirium may be developed as a result of many different conditions. Knowing the cause is very important as delirium may be reversed once the cause is ameliorated.

b. Symptoms of delirium tend to be worse at night and may be minimized by measures such as a calm, constant environment with some light still present at night. Medical management is principally treatment of the underlying cause, however pharmacological treatment may be required to control some of' the acute symptoms (e.g. neuroleptics to limit excessive restlessness and agitation).

Table 1: Causes of delirium

• Effects of exogenous toxins (e.g. alcohol)
• Infection
• Metabolic effects of renal or hepatic failure
• Hypoxia
• Hypoglycemia
• Drugs – Antiparkinsonian medications, overdose of psychotropic drugs
• Electrolyte disturbances
• Stroke, epilepsy, demyelinating diseases, brain tumors, head injury

DEMENTIA

Dementia is chronic brain disorder in which there is progressive decline in acquired intellect, behaviour and personality.

Causes

Causes of dementia are listed in Table 2.

Normal pressure hydrocephalus – A clinically useful division of dementia-producing pathological status is made into two types:

1. *Progressive or fixed,* or irreversible such as Alzheimer's disease
2. *Arrestable or reversible,* such as chronic subdural hematoma or myxoedema.

Investigations in a Case of Dementia

Laboratory tests

- Complete blood count
- Biochemistry profile: Renal and hepatic functions, detect presence of diabetes, and electrolyte abnormalities
- Serum B_{12} levels and folate
- Thyroid stimulating hormone
- Serological tests for syphilis
- HIV testing

Brain imaging

CT scan and MRI – demonstrated large ventricular enlargement, critical sulcal widening and reduced temporal lobe volumes in a significant number of patients with AD.

SPECT – Patients who have bilateral hypoperfusion defect in temporoparietal lobes are more likely to have AD.

Alzheimer's disease is a dementing illness characterised histologically by intracellular neurofibrillary tangles and intracellular amyloid plaques accompanied by neuronal cell loss in certain areas of the brain. There is cerebral atrophy with flattened cortical sulci and enlarged ventricles.

Table 2: Causes of dementia
Parenchymatous brain disease
• Alzheimer's disease (AD)
• Pick's disease
• Huntington's chorea
• Progressive supranuclear palsy
• Lewy body dementia
Vascular causes
• Multi-infarct dementia
• Subcortical vascular dementia
Toxins
• Drugs
• Alcohol
• Analgesics
• Anticonvulsants
• Psychotropic drugs
Infections
• Viral encephalitis
• Neurosyphilis
• Cryptococcus
• Creutzfeldt-Jakob disease
• HIV infection
• Subacute sclerosing panencephalitis
Metabolic
• Chronic hepatic encephalopathy
• Uremia
• Dialysis dementia
• Wilson's disease
Endocrine
• Thyroid, parathyroid, pituitary, adrenal dysfunction
Deficiency
• Pernicious anemia
• Pellagra
• Folic acid and B^{12} deficiency
• Thiamine deficiency
Neoplastic: Brain tumors and other intracranial space occupying lesions
Traumatic
Subdural hematoma, head injury

Aetiology

Age – After 65 years of age, the incidence approximately doubles for every 5-year increase in age; at least until age 90 years. The incidence is similar in men and women but the prevalence is greater in women, reflecting their greater longevity.

Genetics – The risk is about three-fold greater in the first degree relatives of patients with AD. A number of mutations to the early form of AD (before age of 65, presenile AD) have been described in three genes (amyloid precursor protein [APP], presenilin-1 and presenilin-2).

In AD developing after 65, evidence suggests that presence of one copy of the *Apoe* E_4 is associated with a three-fold increased risk of AD, and two copies with a nine-fold increased risk.

Pathogenesis

Plaques are relatively large extracellular structures known as amyloid or amyloid precursor protein (APP). It is a normal protein that plays an essential role in the growth and maintenance of neurons. But in AD, it accumulates abnormally in the brain and interferes with normal brain cell functioning.

Neurofibrillary tangles – Tangles are made of neuronal proteins known as tau proteins, play an essential structural role in holding neurons together. In AD, the proteins break loose from the neurons and form twisted tangles. Findings that tau is heavily phosphorylated and that microtubules are lost in AD have led to a search for regulatory mechanisms of tau phosphorylation as possible cause.

Chemical – Disturbances in cholinergic abnormalities are seen with depletion of acetylcholine as transmitter. Aluminium toxicity is another hypothesis. A gene has been located on chromosome 21.

Clinical Features

Cognitive symptoms – Memory loss is the most common, and usually the presenting complain – Patients have difficulty learning and retaining new information. Later in the disease, remote memories are also affected. Other cognitive defects include anomia, aphasia, apraxia, agnosia and executive planning.

Cognitive deficits relate more clearly to disease progression leading to use of cognitive scales such as Mini-Mental State Examination or Clock Draw Test.

Non-cognitive symptoms – A wide range can occur including disorders of thought content (delusions of theft, infidelity and abandonment, persecutory ideation), disorders of perception (auditory, visual and other hallucinations) and misidentification.

Disorders of affect and behaviour – include depressive symptoms, hypomania, aggression, wandering, agitation, stereotypes, hypersexuality, hypermorality and hyperphagia.

Diagnostic Criteria for Alzheimer's Disease

Probable Alzheimer's disease

- Dementia established by clinical examination and documented by Mini-Mental State Examination or other standard screening test.
- Deficits in two or more areas of cognition.
- Progressive worsening of memory and other cognitive functions.
- No disturbance of consciousness.
- Onset at 40–90 years.
- Absence of systemic disorders or other brain diseases that could account for the progressive deficit memory and cognition.

Possible Alzheimer's disease

- Onset, presentation or clinical course different from that above, but patient has no other disorder sufficient to cause dementia.
- Patient has a systemic or brain disorder sufficient to produce dementia, but this is not considered to be the cause of dementia.

Recognition of Alzheimer's disease

- Loss of memory
- The person might forget what he/she was doing 5 minutes ago and repeat the same thing several times.
- Forgetting words while communicating or finding difficulty in naming objects such as a flower or a dog.
- Difficulty in carrying out daily activities such as dressing, cooking and washing, how to use a knife, open the door, etc.
- Inability to carry out movements despite muscle power and coordination, e.g. tying shoe laces, turning a tap on, fastening buttons or switching on a TV.
- Difficulty in speaking and understanding spoken language. Using language which is difficult for others to understand.
- Inability to recognize people.
- Using a fork instead of a spoon and a knife instead of a pencil
- Personality change. Aggressive and ill-mannered behaviour.
- Frequent mood changes.
- Wandering during day and night, inability to identify time and space.
- Physical change: Weight loss can occur as a result of the person forgetting to chew or swallow.

Management

Cognitive symptoms

1. **Cholinesterase inhibitors**

Donepezil: Reversible long-acting selective piperidine inhibitor of acetylcholinesterase (AChE). Not an inhibitor for butyrylcholinesterase (BuChe). Dose – Initial 5 mg o.d. increased if necessary to 10 mg after 4–6 weeks. Procholinergic side effects.

Rivastigmine – Carbamate which is pseudo-irreversible and intermediate acting. Selective inhibitor for AChE over BuChE but also for AChE in cortex and hippocampus which are most affected in AD. Dose – 1.5 mg b.d. initially, can be increased to 6 mg b.d. over 4-6 weeks and then can be increased to 12 mg b.d. depending on clinical response. Side effects – Nausea, vomiting, diarrhoea, headache, dizziness, abdominal pain, fatigue, malaise, anxiety and agitation.

Galantamine – Dual mechanism of action – Cholinesterase inhibitor with direct nicotine action causing AChE release. Dose – Initial 4 mg b.d. for 4 weeks, then 8 mg b.d. for at least 4 weeks and then can be increased to 12 mg b.d. depending on clinical response. Side effects – Nausea, vomiting, diarrhoea. Contraindicated in patients with hepatic, renal impairment.

2. **Memantine hydrochloride** – Acts by attaching to NMDA receptors in the brain and regulating activity of glutamate, helping to ensure that the right amount of glutamate is available by allowing calcium to flow in the nerve cell for the brain to process, store and retrieve information, resulting in learning and memory. Can be given in combination with donepezil for maximum benefit. Dose – 1st week 5 mg o.d., 2nd week 5 mg b.d., 3rd week 10 mg morning, 5 mg evening, 4th week 10 mg b.d. Side effects – Dizziness, confusion, headache, constipation.

Non-cognitive symptoms: Non-pharmacological treatment, particularly if symptoms not severe. (a) Assessment of clear precipitants (e.g. suboptimal prompting, personal care or toileting), social interaction, activity, exercise. (b) Use of specific drugs is based on psychiatric treatment in younger patients and avoidance of drugs with marked anticholinergic properties.

Depressive symptoms: Non-tricyclic antidepressants (e.g. selective serotonin re-uptake inhibitors, trazodone, escitalopram).

Psychotic symptoms: Atypical antipsychotics (e.g. risperidone, olanzapine).

Aggressive symptoms: Atypical antipsychotics, non-tricyclic antidepressants or anticonvulsants (e.g. carbamazepine, valproate).

Agitated behaviours: Atypical antipsychotics, non-tricyclic antidepressants or, in severe cases, short-acting benzodiazepines.

ORGANIC AMNESTIC SYNDROME

Clinical features: Memory impairment due to organic cause, consciousness intact and unlike dementia, no disturbance of attention or of global intellectual function, abstract thinking or personality. Impairment of memory is both for recent or long-term memory. Immediate memory is not disturbed.

Diagnosis (ICD-10)

- Recent memory impairment; anterograde and retrograde amnesia
- No impairment of immediate retention and recall, attention, consciousness and global intellectual functioning
- Historical or objective evidence of brain disease or injury (especially with bilateral involvement of diencephalic and medial temporal structures).

Transient global amnesia is a syndrome with abrupt onset with loss of memory probably due to transient cerebral ischemia involving posterior cerebral circulation.

Causes:

- Thiamine deficiency most commonly due to chronic alcoholism (Wernicke-Korsakoff syndrome)
- Lesion involving inner core of limbic system bilaterally, e.g. head injury, hypoxia, bilateral posterior cerebral artery infarction, herpes simplex encephalitis, neoplasm in region of 3rd ventricle, bilateral temporal lobectomy.

Management – Supportive care and treatment of causative condition.

COGNITION AND COGNITIVE TESTING

Cognition is the acquisition and manipulation of knowledge and is a cardinal function of the human brain. Cognitive function can be assessed using a problem-oriented approach (e.g. specific language tasks in suspected aphasia), or a non-problem oriented number of screening tests. Ideally, both methods should be used to assess cognitive disorders.

Non-problem oriented screening has the advantage of providing a numerical score that allows comparison with other patients and monitoring of progress. The Folstein Mini-Mental state examination is the most common bedside cognitive test (Table 3). It gives a score out of 30; 24 or less is generally considered abnormal and is highly suggestive of a cognitive disorder.

Table 3: Folstein Mini-Mental state examination

Orientation	Maximum score
• Can you tell me today's date, month and year? (accept date if correct to within 2 days)	5
• Which day of the week is it today?	
• Can you also tell me which season it is?	
• What city/town are we in?	5
• What county and country?	
• What building are we in, and on what floor?	
Anterograde memory	
• I would like you to remember three objects (name three common objects, e.g. ball, car, man)	3
• Can you repeat the words I said? (score 1 for each word, repeat up to six trials until all three are remembered, record number of trials needed)	
Attention and calculation	
• Starting with 100, keep subtracting 7 (stop after 5 answers - 93, 86, 79, 72, 65; do not penalize for sequential errors - e.g. 92, 85, 78, 71, 64 scores 4) or Spell word backwards ('drlow' scores 4, 'dw' scores 2)	5
Recall	
• What were the three words I asked you to say earlier? (omit this test if the patient failed to remember all three objects during the registration test)	3
Language	
Naming	
• Name these objects (show a watch, show a pencil)	2
Repeating	
• Repeat the following: "No ifs, ands or buts"	1
Repeating	
• Read this sentence and do what it says (show card or write 'close your eyes)	1
Writing	
• Now can you write a short sentence for me? (it must contain a subject, verb and object)	1
Three-stage command	
• Can you take this piece of paper in your left (or right) hand, fold it in half, and put it on the floor?	3
Visuospatial	
• Can you copy this drawing? (both pentagons must have five sides and must be interlocked; do not penalize for poor artistic quality)	1
Total score	**30**

Problem-oriented Screening

History – Much information can be gained from spontaneous conversation with the patient. Non-fluent, effortful speech punctuated by frequent pauses may suggest a Broca's-type aphasia. If fluent but vacuous and circumlocutive as in Wernicke's aphasia or the fluent anomia accompanying Alzheimer's disease.

Episodic memory can be anterograde (acquisition of new memories) or retrograde. It is useful to recount their own medical and social history, including dates and locations of home, schooling, employers, marriages and births of children.

Orientation and attention – Recent onset of severe disorientation (details of time, place and person) is typical of metabolic encephalopathy and examiner should check for asterixis ('metabolic flap').

Digital span is a simple assessment of attention; normal individuals have a forward span of at least six digits, and reverse span of one or two fewer. Digits must be presented individually, by reading the string to be repeated at a rate of one digit per second.

Ability to preserve at a given task is another means of assessing attention. Patient is asked to recite the months of the year in reverse order or to copy a design.

Language Dysfunction is an early feature of AD that manifests particularly in naming tasks. This results in circumlocutive language, e.g. when shown a drawing of a kite, a patient may reply: 'that's a thing that flies'. Wernicke's and Broca's aphasia are seen after stroke.

Memory: Long-term memory may be divided into personal recollections (episodic memory) and shared knowledge of the world (semantic memory). Testing semantic memory, in terms of knowledge of famous people and events. Breakdown in semantic memory also manifests as an inability to name objects or drawings, and to make broad, superordinate responses (e.g. 'animal' for 'elephant').

Knowledge of recent news events (after disease onset) provides an insight into retrograde memory function. Three trials of a name and address followed by a 5-minute recall condition also assesses efficiency of registration. Increased forgetting after a 5-minute delay is highly suggestive of amnestic syndromes (e.g. AD).

Visuospatial – Hemispatial neglect is demonstrated by 'sensory extinction or clock-drawing' and is usually a feature of non-dominant parietal lesions.

Executive function concerns high-order brain function (e.g. problem solving, reasoning, mental abstraction) that rely on the dorsolateral prefrontal lobes. Frontal lobe disorders are also associated with impulsivity and failure to persevere with tasks.

Tests – Letter fluency test – Patients are given 1 minute to produce as many words as they can beginning with a single letter. Normal individuals usually produce 15 or more words. Patients with disorders of executive function struggle to produce many words.

'Go-on-go' test assesses impulsivity. Patient is asked to tap the table once if the examiner does so, but not at all if the examiner taps twice. Patients with frontal pathology are often unable to stop themselves tapping under both conditions.

4. PSYCHOSIS

Psychosis is a mental disorder in which a person's mental capacity, emotional responsivity, capacity to recognise reality and to communicate and relate to others is sufficiently impaired so as to interfere with his or her ability to deal with the ordinary demands of life.

TYPES OF PSYCHOTIC DISORDERS

See Table 4.

I. *Organic psychosis* (Organic brain disorders).
II. *Functional psychosis:*
    1. Schizophrenia
    2. Schizophreniform disorder
    3. Brief psychotic disorder
    4. Schizoaffective disorder
    5. Delusional disorders

ORGANIC PSYCHOSIS

Clinical Manifestations

Symptoms of organic brain disorders can be divided into:

1. *Mandatory or essential symptoms* which are seen in every case of organic psychosis.
2. *Obligatory or accessory symptoms,* which are dependent on certain factors peculiar to the individual patient, i.e. his/her personality, emotional conflicts and stresses, environmental situation and interpersonal relationships.

Mandatory Symptoms

1. *Impairment of orientation in time, place and/or person.*
2. *Impairment of memory* – Memory for recent events is impaired first, while memory for remote events may be unaffected until an advanced stage of the disease process.

Table 4: Differences between organic and functional psychosis

Organic	*Functional*
• Caused by or associated with impairment of brain tissue function; evidence for systemic diseases involving brain, liver, kidney, endocrine glands, etc. present.	• Caused usually by psychological factors. No clearly systemic cause or structural change in brain or defined other viscera.
• Disturbances of consciousness common.	• Disturbances of consciousness are rare.
• Disturbances of orientation, memory and intelligence present.	• Disturbances of orientation, memory and intelligence absent. (Pseudo disturbances which arise because of patient's non-cooperation and lack of attention or interest may be present).
• Disturbances of perception, viz. hallucinations are of visual variety.	• Disturbances of perception, viz. hallucinations are usually of auditory variety.
• Disturbances of emotions are usually of the "labile" type, i.e. patient fails to hold back emotional expressions – "emotional incontinence".	• Emotional incontinence is rare.
• Confabulation common.	• Confabulation rare.
• Physical examination of the patient reveals clinical features of systemic diseases.	• Physical examination of the patient usually reveals no abnormality which can explain the mental symptoms.
• Psychological tests like Bender-Gestalt test positive. Marked difference between verbal and non-verbal tests of intelligence.	• Bender-Gestalt test negative. No marked difference between verbal and non-verbal tests of intelligence.
• Laboratory and radiological investigations as well as electroencephalography help in determining the etiological factors responsible for the psychosis.	• Laboratory and radiological investigations as well as electroencephalogram reveal no specific abnormality.

3. *Impairment of intellectual functions* – A variety of intellectual functions may be disturbed, e.g. calculation, comprehension, general fund of information, ability to learn new tasks and ability to understand the meaning of verbal language (vocabulary).
4. *Impairment of consciousness* of varying degree, ranging from stupor, clouding of consciousness to coma.
5. *Altered emotionality-emotional lability,* i.e. patient shifts rapidly from one emotion to another or he may lose contact over his emotions – emotional incontinence.

Obligatory or accessory symptoms – Anxiety, depression, psychotic symptoms, avoidance of situations, denial of cognitive defects, jocularity, confabulation, circumstantiality, excessive orderliness.

Investigations

1. *Laboratory* – Haematological, bio-chemical, serological tests, mainly to confirm clinical diagnosis of systemic disease.
2. *Radiological* – X-ray studies, isotope scanning, CT scan, angiography, MRI.
3. *Others* – EEG, CSF analysis.
4. *Neuropsychological tests* – to assess higher mental functions – Wisconsin card sorting test, Bender-Gestalt visual motor-coordination test; Wechsler memory scale and intelligence tests. In the latter the score on performance or non-verbal sub-tests is lower than score on verbal sub-tests by at least 15 points.

Types of Organic Brain Disorders

***Acute*:** Characterised by: (a) Sudden onset with rapid development of impairment of orientation, memory, intellectual functions, judgment and affect. (b) Delirium, stupor or coma may be present. (c) It is caused by temporary, reversible and diffuse disturbance of brain tissue function. (d) Patient may recover without any residual defect, or may progress to the chronic type. The clinical course usually progresses over months or years and the syndrome may end with death.

***Chronic*:** Characteristics are: (a) Onset is usually insidious. (b) Gradual deterioration of higher mental functions. (c) It is caused by an irreversible, permanent and diffuse alteration of brain tissue function. (d) The clinical course usually progresses over months or years and the syndrome may end with death. Although the causative factor can be identified and eliminated at times, some permanent alteration in higher mental functions may remain.

2. FUNCTIONAL PSYCHOSIS

A. Schizophrenia

Kraepelin in 1896 recognised this form of illness and coined the term "Dementia Precox" (premature deterioration of mental faculties). Bleuler in 1911 introduced the term schizophrenia (splitting of mind) to identify the same illness.

Histopathological studies of the brains of patients of schizophrenia have revealed cytoarchitectural changes consistent with impairment of neurodevelopment at an

early age. Minor physical anomalies (e.g. malformed ears, hands or palate), representing alterations in ectodermal development as a result of early neuronal deviance are also more common in schizophrenia.

Risk Factors

Genetic factors – Lifetime risk of developing schizophrenia rises from less than 1% in the general population to about 10% in first-degree relatives of patients with the disease, and upto 48% in the children of two schizophrenic patients. Risk of schizoaffective disorder, schizotypal personality disorder and affective psychosis is also greater in relatives of schizophrenics. If one parent has it then the child has 16% chance.

Early environmental factors – Obstetric complications appear to be important in mothers of schizophrenics (e.g. during pregnancy, pre-eclampsia, antepartum hemorrhage), and difficulties during labour (e.g. protracted labour, asphyxia, low birth weight) than normal controls and patients with other psychiatric disorders. Epidemiological studies have found an association between maternal exposure to influenza epidemics in the second trimester and increased rate of schizophrenia in offspring.

Precipitating factors – The first psychotic breakdown often follows an adverse life event, or drug abuse and dependence.

Neurochemistry – Dopaminergic overactivity was originally proposed as the neurochemical substrate for schizophrenia, based on the mode of action of antipsychotic drugs which block post-synaptic dopamine (D_2) receptors. In view of serotonergic (SHT_2) receptor blocking properties of the newer atypical neuroleptic drugs, serotonergic system have also been implicated.

Clinical Presentation

Acute schizophrenia

Delusions – are the most common symptoms. They may be persecutory, grandiose, religious or hypochondriacal, and occasionally extremely bizarre.

Passivity phenomena – Sufferers believe that impulses, actions, emotions or sensations they experience are not their own but imposed on them by external forces.

Hallucinations – are usually auditory. The duration of hallucinations is as important as their content or form, because the duration tends to be longer in patients with schizophrenia than in other psychoses.

Thought disorders – occur in about 20%. Speech may appear odd; patients may give apparently irrelevant answers to direct questions, may jump from one theme to another with no cohesive link (loosening of associations), and occasionally use ordinary words in new way (paraphasia) or invent new words (neologisms). Sometimes speech is totally incomprehensible, comprising a jumble of unrelated words ('word salad').

Mood – Patients may feel that the world around them has changed in some way (perplexity, delusional mood), or may show flattening of emotional response (blunted effect), or incongruity of mood. Depressive or manic symptoms may also occur.

Catatonic phenomena (e.g. mutism, stupor, strange postures or movements) are uncommon.

Chronic schizophrenia – In this type, symptoms are present for a continuous prolonged period of more than 2 years. The predominant symptoms are 'negative' or non-productive. These include lack of initiative and drive, poverty of speech, social withdrawal and blunting of emotional expression. Depression is a common feature. Acute psychotic episodes can recur from time to time, precipitated by withdrawal of medication or stressful life events.

Diagnosis – Schneider's first-rank symptoms are incorporated in the current definitions in WHO International Classification of Diseases (ICD-10) which requires:

- Clear evidence of past or present psychosis
- Absence of prominent affective symptoms
- Minimum duration of illness at least 1 month.

Schneider's First-rank Symptoms of Schizophrenia

- Auditory hallucinations
  - Third person talking or arguing about the patient
  - Third person commentary on patient's actions

Audible thoughts

- Thought withdrawal or insertion
- Thought broadcast
- Somatic passivity
- Feelings or actions experienced as being under external control
- Delusional perception

Note: First-rank symptoms occasionally occur in mania, drug-induced psychosis.

Subtypes of Schizophrenia (ICD-10), see Table 5.

Table 6 gives the differential diagnosis of schizophrenia.

Table 5: WHO international classification of diseases subtypes of schizophrenia

Subtype	*Main characteristics*
• Paranoid	Prominent delusions and hallucinations Personality well preserved
• Hebephrenic (Disorganised)	Thought disorder, affective changes, mannerisms, early onset, poor prognosis
• Catatonic	Psychomotor disturbance (e.g. posturing, stupor)
• Undifferentiated	No early predominant symptoms
• Post-schizophrenic depression	Depressive episode arising in aftermath of schizophrenic illness
• Residual	Clear progression from earlier psychotic stage to defect state of negative symptoms
• Simple	Progressive deterioration and eccentricity in absence of overt psychosis

Table 6: Differential diagnosis of schizophrenia

Organic	*Functional*
• Temporal lobe epilepsy • Drug-induced states (amphetamines, cocaine, LSD, cannabis) • Alcoholic hallucinosis • Cerebral tumour • Encephalitis • Head injury	• Affective disorder • Schizoaffective disorder • Atypical psychoses and other paranoid states • Personality disorders

Table 7: Prognostic factors in schizophrenia

Good	*Bad*
Older age at onset	Younger patient
Married	Single, separated, widowed, divorced
Short duration	Long duration
No family history	Family history of schizophrenia
Good social relationships	Social isolation
Stable work record	Poor work record
Good psychosexual adjustment	Poor psychosexual adjustment
No previous psychiatric history	Previous psychiatric history
Known precipitating cause	No obvious precipitating cause
Acute onset	Gradual onset
Prominent affective symptoms	No affective symptoms
Catatonic symptoms	Paranoid symptoms
Initiative and drive preserved	Loss of initiative and drive
No neurological signs	Presence of 'soft' neurological signs
Minimal negative symptoms	Predominant negative symptoms
Prompt treatment	Delayed treatment

Prognosis

Prognostic factors in schizophrenia are given in Table 7.

Management

Antipsychotic drugs – In the early acute phase, treatment has a dual purpose – control of agitated or aggressive behaviour (achieved by the sedative action of the drug within minutes or hours), and alleviation of psychotic symptoms (within days or weeks).

Once patient is stabilized, maintenance therapy to prevent development of further symptoms is continued with an oral or depot formulation. Maintenance treatment should be continued at the lowest possible dose for at least 1 year after the first schizophrenic episode. In recurrent episodes, maintenance therapy can be continued indefinitely. Failure to respond to medication may require ECT therapy. However with the advance of new medication, the need for ECT is reduced.

Certain forms of psychotic therapy may be beneficial to the patient in the recovery phase along with occupational therapy and vocational help.

Psychological and social management – Family intervention has been shown to reduce risk of relapse associated with high levels of expressed emotion. New cognitive behavioural techniques can be used effectively with drugs to reduce distressing symptoms (e.g. auditory hallucinations) or to help patients develop an insight into their illness.

5. MOOD DISORDERS

The mood disorders are so called because their main feature is an abnormality of affect on mood. Episode of clinically disturbed mood can be divided into manic and depressive phases. Over a patient's lifetime, the two types may occur in varying patterns. There is therefore a 'lifetime diagnosis' to be made in recurrent disorders, in addition to diagnosis of each individual episode.

DIAGNOSIS OF EPISODE

Manic episode – is almost the opposite of depression. Mood is often euphoric or elated to a degree disproportionate to the patient's circumstances, and can be irritable, hostile or aggressive. Energy levels are raised, and many feel they do not need to sleep. There are grandiose

ideas and frank delusions. They often become involved in sexual or financial indiscretions and fail to accept the likely consequences of actions.

Depressive episode – Clinical features include symptoms that almost always occur (e.g. depressed mood, loss of interest and pleasure, reduced energy) and other symptoms. Within this general depressive syndrome, some symptoms (termed 'biological', 'somatic' or 'vegetative') have special significance – they indicate the presence of 'endogenous' or 'melancholic' depression. These symptoms include anhedonia (complete inability to take interest or pleasure in anything, leading to a flat or unvarying mood), some psychomotor symptoms (retardation, agitation) and marked loss of appetite, weight and libido.

Symptoms of depression (*see* Table 8) – The episode can vary from mild to severe, depending on the number and severity of symptoms and on the disturbances they cause to work and family commitments. Depression is commonly associated with symptoms of anxiety or with coexisting anxiety disorders such as agoraphobia or social phobia.

Hallucinations and delusions may occur in severe cases when these symptoms are present, the illness is termed 'psychotic depression'.

Depression can generally be distinguished from other syndromes when four or more symptoms of a depressive episode are present.

CRITERIA FOR A DEPRESSIVE EPISODE

A to D must all apply

Table 8: Symptoms of depression

General	*Somatic*
• Hopelessness	• Appetite disturbance
• Helplessness	• Weight change
• Low mood	• Constipation
• Low self-esteem	• Amenorrhoea
• Reduced energy	• Low libido
• Suicidal thoughts	• Sleep disturbance
• Loss of interest	
• Poor concentration	*Anxiety*
• Guilt	• Tension
• Pessimism	• Apprehension
• Depersonization	• Phobias

A

At least 5 or more of the following symptoms (including 1 or 2) present for at least 2 weeks, representing a change from previous functioning.

1. Depressed mood almost every day for most of the day.
2. Markedly reduced interest or pleasure in all, or almost all activities almost every day for most of the day.
3. Significant weight. loss or weight. gain when not dieting, or increased or decreased appetite almost every day.
4. Insomnia or hypersomnia almost every day.
5. Agitation or retardation almost every day.
6. Fatigue or loss of energy almost every day.
7. Feelings of worthlessness or excessive or inappropriate guilt almost every day.
8. Reduced ability to think or concentrate or indecisiveness almost every day.
9. Recurrent thoughts of death or suicide.

B

1. No organic cause
2. Not caused by bereavement

C

No delusions or hallucinations in absence of mood symptoms for as long as 2 weeks during the course of the illness.

D

Not superimposed on schizophrenia or other psychoses.

'Atypical' depression – Definition of a depressive episode includes some symptoms representing changes in function that are opposed to the 'typical' somatic symptoms. When these dominate, the syndrome is termed 'atypical' depression. Such patients suffer from an increase in appetite and weight (often with carbohydrate craving), hypersomnia, fatigue and a reversed diurnal variation in mood, which is at its worst later in the day. This pattern of symptoms is often found in patients with a winter pattern in their illness (seasonal affective disorder).

Masked depression – Patients with a depressive disorder may present with somatic symptoms (e.g. headache, backache), sometimes they appear to be unaware of being depressed, even when they have a complete set of somatic symptoms with no physical cause.

Lifetime diagnosis – Over the patient's lifetime episodes of mood disorder occur in one of three broad patterns:

Bipolar disorder – Here patients suffer from episodes of depression and of mania at various times. Progression of the disorder may be regular, cyclical or periodic, but is

usually irregular, each bout striking 'out of the blue' with no clear pattern. Both manic and depressive episodes can be triggered by life events. Recurrent depressive disorder that may be predictable (e.g. in seasonal affective disorder) or irregular. Symptoms may be similar in each episode or may vary over the years.

Recurrent depressive disorder – Recurrent episodes that may be predictable (e.g. in seasonal affective disorder) or irregular symptoms may be similar in each episode or vary over the years. Also referred to as Major depressive disorder - Recurrent.

Persistent mood disorder – In cyclothymia, mood swings occur for much of the time but are milder than manic depression. In dysthymia, patients experience persistent low grade depression.

Secondary mood disorders – The illnesses described above are assumed to be primary; they are not caused by another illness. Mood disorders thought to result from a physical illness (e.g. Cushing's disease, carcinoma) or a previously identified psychiatric illness (such as schizophrenia or alcoholism) are termed secondary mood disorders.

AETIOLOGY

Genetic factors – play a major role in mood disorders and their effect is stronger in patients with more severe biological symptoms. In twin studies of bipolar disorder, average concordance rate is 65% in monozygotic twins and 14% in dizygotic twins. An inherited factor, not an environmental one, determines the high rates seen in first degree relatives.

Social factors – Events associated with depression are generally 'loss events' such as loss of a job, relative or friend, money, health or status. Other factors that adversely affect the response to the events can be – A working class background, lack of confiding relationship with a spouse, unemployment, loss of a parent before 11 years of age. The presence of significant symptoms before onset of depressive illness occurs with somatic symptoms as much as those without. Thus the so called endogenous depression does not necessarily occur 'out of the blue'.

Biological markers for depression – show strong associations, particularly with the somatic (endogenous) syndrome. False-positive results occur in the presence of various medical disorders.

Dexamethasone suppression test – is the most important biological marker. A small dose of the drug is given postoperatively in the evening and plasma cortisol is measured at the same time the next day. Failure to suppress endogenous cortisol secretion below a given reference point is associated with endogenous depression, particularly in patients with weight loss. This abnormality reflects underlying hyperactivity of the hypothalamo-pituitary-adrenal axis.

Abnormal a_2 receptors of the hypothalamus – Failure of clonidine (an a_2-agonist), to provoke secretion of growth hormone is a consistent finding in depressed patients. The response returns temporarily with antidepressant treatment, but subsequently becomes abnormal again. This suggests that patients who have been depressed have an enduring abnormality in the a_2 receptors of the hypothalamus. This test is abnormal only in patients with endogenous depression.

5-HT challenge test – Tryptophan, taken orally, releases prolactin and growth hormone by increasing the activity of serotonergic system. The response is reduced in depression.

Circadian rhythms and related markers – have also been found abnormal in depression. This is suggested by the diurnal variations in mood, early morning waking and the sometimes periodic course, for example, yearly attacks of illness. Abnormalities of circadian rhythms of cortisol and melatonin have been reported, and sleep EEG reveals that the first phase of rapid eye movements sleep occurs earlier than expected.

Psychological factors – Repeated trauma, stressful life events and disturbed marital and interpersonal relationships.

MANAGEMENT

Pharmacotherapy – Severe type mood disorders are more responsive to physical treatment.

Antidepressants – are used in all phases of the treatment of major depression, acute management, continuation therapy and maintenance or prophylactic treatment.

Tricyclic drugs – increase recovery rate significantly, but have a wide range of side effects. These lead to non-compliance and limit usefulness in illnesses of mild to moderate severity. The dose of tricyclics should be initially low and increased gradually.

Selective serotonin re-uptake inhibitors (SSRIs) are effective drugs and are better tolerated at therapeutic doses than other compounds.

Table 9: Drugs for treatment of mood disorders

Drug	*Indications*
Antidepressants	
• Tricyclics • Selective serotonin re-uptake inhibitors • Monoamine oxidase inhibitors	Acute treatment, Continuation therapy and maintenance of major depression Atypical vegetative symptoms of depression
Antipsychotics	
Conventional (haloperidol) Atypical (olanzapine)	Acute treatment of mania
Mood stabilizers	
Lithium Carbamazepine Valproate Lamotrigine Gabapentin	Acute treatment of mania Prophylaxis of bipolar disorder Treatment of resistant depression

Table 10: Adverse effects of tricyclic antidepressants

Pharmacological action	*Adverse effects*
Anticholinergic	Dry mouth, tachycardia, blurred vision, glaucoma, constipation, urinary retention
α-adrenergic blockers	Drowsiness, postural hypotension, sexual dysfunction, cognitive impairment
Histamine H_1 receptor blockade	Drowsiness, weight gain
Membrane stabilizing properties	Cardiac conduction defects, arrhythmias, epileptic seizures
Others	Rash, oedema, leucopenia, elevated liver enzymes

Table 11: Adverse effects of selective serotonin re-uptake inhibitors

GI	*CNS*
Common	*Common*
Nausea	Headache
Appetite loss	Insomnia
Dry mouth	Dizziness
Diarrhoea	Anxiety
Constipation	Fatigue
Dyspepsia	Tremor
Uncommon	*Uncommon*
Vomiting Wt. loss Others	• Extrapyramidal reactions • Seizures • Mania
Common	*Uncommon*
Sweating	Rash
Delayed orgasm	Pharyngitis
Anorgasmia	Serum sickness
	Hyponatremia
	Alopecia

DRUGS USED IN TREATMENT OF MOOD DISORDERS

See Table 9.

Mechanism of action – All these drugs can potentiate the activity of noradrenaline and/or 5-HT in the CNS, usually by inhibiting re-uptake of these amines into the nerve endings. Though pharmacological effect is apparent a few hours after starting treatment, but most patients require a couple of weeks before the effect of antidepressant treatment is fully apparent.

Efficacy – In most depressed patients the drugs mentioned are equal in efficacy. In more severely depressed patients drugs that cause potentiation of both 5-HT and noradrenaline neurotransmission (e.g. amitriptyline, clomipramine, venlafaxine, citalopram) are the most efficacious. In patients with depressive psychosis, antidepressants are usually not effective as a sole treatment, and should be given with an antipsychotic. ECT is an alternative approach.

Adverse effects – Most tricyclic antidepressants are potent antagonists of muscarine, histamine H_1 and α_1-adrenoreceptor, and have characteristic side effects (Table 10). Some antidepressants (trazodone, mirtazapine) have a sedative effect in absence of anticholinergic properties.

The acute pharmacological action of SSRIs is essentially confined to blockade of 5-HT uptake and is associated with side effects such as anxiety, insomnia and sexual dysfunction different from those with tricyclics. Adverse effects of selective serotonin re-uptake inhibitors are listed in Table 11.

Long-term treatment – Continuation of antidepressant drugs for 4–6 months after resolution of symptoms is associated with significantly lower rate of relapse.

Discontinuation symptoms – Abrupt cessation of tricyclic antidepressants can provoke withdrawal symptoms like abdominal pain, nausea and diarrhoea, fragmented sleep and nightmares. Discontinuation symptoms can also occur 24–72 hours after sudden cessation of SSRIs particularly paroxetine; common withdrawal symptoms are dizziness, nausea, lethargy and headache.

Monoamine oxidase inhibitors (MAOIs) have the major disadvantage of adhering to a tyramine-free diet to avoid the hypertensive crisis of the so-called cheese reaction. Principal MAOIs in use are phenelzine (45–90 mg) and tranylcypromine. (These are not available in India). Side effects are similar to those of tricyclics; postural hypotension can be troublesome. They are selectively useful in patients with the atypical vegetative symptoms of depression.

Reversible MAOIs such as moclobemide are less likely to cause cheese reaction.

Mood-stabilizing drugs

Lithium is used in treatment of several conditions:

- First-line agent in acute treatment of mania (often in combination with antipsychotic drugs in severe illness) and in long-term prophylaxis of bipolar disorder.
- Prophylaxis of recurrent unipolar depression though agent of first choice is tricyclic or a newer antidepressant.
- Useful antidepressant action when added to the antidepressant drug treatment of patients who have failed to show a satisfactory response to them.
- In patients with learning disabilities, lithium decreases aggressive behaviour towards self or others.

Monitoring of lithium levels is necessary because renal lithium clearance varies widely between individuals, and the dose required for optimal therapeutic effect is only slightly less than that resulting toxicity; permanent renal and cerebral damage can occur if toxicity is unrecognised (*see* Table 12). Several drugs, e.g. diuretics, NSAIDs, ACEIs, metronidazole can raise lithium levels and cause toxicity.

Plasma levels of lithium (12 hours after the final dose) necessary for prophylaxis should be in the range of 0.5–0.8 mmol/L. Some patients require levels similar to those for acute management (0.9–1.2 mmol/L) for adequate prophylaxis.

Side effects – Lithium has a wide range of side effects and hence compliance for the drug is poor. Patients most often complain of tremor, thirst, memory difficulties, weight gain and tiredness.

Abrupt cessation of lithium in bipolar patients is associated with increased risk of affective relapse.

Carbamazepine – Many patients with bipolar disorder or mixed affective states do not respond satisfactorily to lithium. Carbamazepine may produce good mood-stabilizing effects when given alone or with lithium. The drug can be useful also in acute treatment of mania, and can be combined with lithium or antipsychotic drugs. Dose 400–1200 mg daily. Adverse effects. Carbamazepine levels can be increased by erythromycin, SSRIs and nefazodone.

Sodium valproate is effective in patients with acute mania and in those with mixed affective symptomatology. An advantage of valproate in acute mania is the possibility of rapid dose increase, resulting in rapid onset of therapeutic effect in 2 days with loading dose of 20 mg/kg/day.

Antipsychotic drugs – Despite the availability of mood-stabilizing drugs, antipsychotics continue to be used because of their ability to produce rapid sedation and control of overactivity and aggression. As in the treatment of schizophrenia, current practice is to use lower doses of antipsychotics to treat mania (e.g. haloperidol 5–10 mg daily).

Table 12: Adverse effects of lithium, carbamazepine and valproate

	Lithium	*Carbamazepine*	*Valproate*
Neurological	Tremor, weakness, dysarthria, ataxia, impaired memory	Dizziness, weakness, drowsiness, ataxia, headache, visual disturbance	Tremor, sedation
Renal / fluid balance	Increased urine output with decreased urine-concentrating ability, thirst, oedema	Low sodium states, oedema	
GI/hepatic	Altered taste, anorexia, nausea, vomiting, diarrhoea, wt. gain	Anorexia, nausea, constipation, hepatitis	Anorexia, nausea, vomiting, diarrhoea, wt. gain, hepatitis
Endocrine	Decreased thyroxine with increased TSH, goitre	Decreased thyroxine with normal TSH	Menstrual disturbances
Haematological	Leucocytosis	Leucopenia	Low platelet count, abnormal platelet aggregation
Dermatological	Acne, exacerbation of psoriasis	Erythematous rash	Hair loss
CVS	ECG changes (usually benign)	Cardiac conduction disturbances	

Patients with bipolar illness are commonly given longer-term antipsychotic medication because this may help prevent swings in mood. The risk of tardive dyskinesia is less likely with clozapine and olanzapine.

ECT – is an effective and fast-acting treatment for severe mood disorders, but its use is generally reserved for patients unresponsive to antidepressant drugs or when the need for clinical response is particularly urgent.

Indications for ECT

- Major depression not responding to antidepressant drugs with:
  - Psychotic symptoms
  - Failure to eat and drink
  - Depressive stupor
  - High risk of suicide
- Schizoaffective depression
- Mania not responding to drug treatment
- Postpartum affective psychosis

Duration of treatment and maintenance therapy – Usually 6 to 10 ECTs are effective in resolving acute depression or mania. Once the course of treatment is completed appropriate prophylactic drug treatment should be given to prevent relapse. Some patients with frequent relapses that respond to ECT can be considered for maintenance ECT, in which treatment is given every 2 weeks or monthly.

Psychological treatments – These can be used in patients with 'real' problems such as threatened redundancy or a relationship difficulty. Many depressed patients perceive imagined problems and here techniques used in cognitive psychotherapy can be useful.

6. PSYCHONEUROSIS OR NEUROSIS

(Anxiety disorders, somatoform disorders, dissociative disorders)

A group of mental disorders which are sometimes described as "minor" or "benign". The patient's symptoms do not interfere with his capacity for insight and judgement, his ties with reality are intact, and his mental dysfunctions are comparatively of a milder form in contrast to psychosis. As in functional psychosis, in these disorders also, there is no clearly defined structural change in brain tissue function to account for the symptoms. *See* Table 13 for the differences between psychosis and neurosis.

ANXIETY DISORDERS

Anxiety is a normal response to threat or stressful events, and is usually short-lived and controllable. It probably functions as an 'alarm mechanism' to prepare an individual for a physical response to perceived danger (the 'fight-or-flight' response). Anxiety symptoms are considered clinically significant when they:

- Are abnormally severe
- Are unusually prolonged
- Occur in absence of stressful circumstances
- Impair physical, social or occupational functioning

Features of anxiety – Anxiety symptoms may be a feature of some physical conditions (e.g. caffeinism, drug withdrawal, hyperthyroidism, hypoglycemia, paroxysmal tachycardia, complex partial seizures, pheochromocytoma) and these must be excluded when features in the history or physical examination suggest their presence. *See* Table 14 for the classification of anxiety features.

Generalized anxiety disorder – is characterized by inappropriate or excessive anxiety and worrying that is persistent (more than 6 months) and not restricted to particular circumstances (i.e. it is 'free-floating'). Common features are listed in Table 15.

Differential diagnosis – Most important is depressive illness, for this patient is questioned about symptoms such as loss of interest and pleasure, loss of appetite and weight, diurnal variation in mood and early morning waking.

A distinction is also made between patients with and without panic attacks.

- Panic attacks may accompany any anxiety disorder, but a specific diagnosis of panic disorder can be made if they occur frequently and unexpectedly.
- Phobic disorders are divided into specific (simple) phobias, agoraphobia and social phobia.
- Obsessive compulsive neurosis is a distinct entity, but at present is grouped with other neurotic, stress-related and somatic disorders.

Management – Definitive need for treatment depends on severity of symptoms, degree of personal distress, level of occupational and social impairment.

a. Benzodiazepines are effective anxiolytic drugs but can cause sedation and have potential for dependence. They should be given in short courses. (b) Other drugs include certain tricyclic antidepressants (e.g. imipramine 50–300 mg/d), buspirone (5-HT_{1A} partial agonist) (15–45 mg/d) and venlafaxine (serotonin-noradrenaline re-uptake inhibitor 75 mg/d), sertraline

Table 13: Differences between psychosis and neurosis

	Psychosis	*Neurosis*
Aetiology:		
Biological factors	More important	Less important
Environmental factors	Less important except in reactive psychosis	More important
Psychopathology:		
Personality disintegration	Severe	Partial
Clinical manifestations:		
1. Touch with reality.	Lost	Not lost
2. Insight into the illness	Lost (Patient believes that he is all right but family members and relatives are sick)	Not lost (Patient complains of illness but family members and relatives believe that the patient is not sick)
3. Judgement (i.e capacity to discriminate between right and wrong, good and bad, ethical and unethical).	Lost	Not lost
4. Social relationship and behaviour.	Affected	Not affected
5. Personal hygiene.	Neglected	Not neglected
6. Disturbances of mental functions like thinking, emotion and behaviour.	Gross	Minor
7. Disturbances of intelligence, memory, attention, consciousness and orientation.	Common in organic psychosis	Rare
8. Disturbances of thought (viz. delusions) and perception (viz. illusions and hallucinations).	Common	Rare
Course and prognosis	More malignant than benign. Difficult to treat. Recovery may not be always possible or complete. Relapses are common.	More benign than malignant. Easier to treat. Recovery is complete. Relapses are common.
Management		
1. ECT	Very useful	Contraindicated
2. Abreactive therapy	Not useful	Useful
3. Drugs	Neuroleptics commonly used.	Anxiolytics and antidepressants
4. Psychotherapy		
a. Supportive	Useful	Useful
b. Analytical	Not useful	Useful
5. Case work	Useful	Useful

(selective serotonin re-uptake inhibitor, 5 mg/day) none of which have the same potential for psychological or physical dependence.

b. Behaviour therapy in the form of relaxation training, systemic desensitization and cognitive therapy. Psychotherapy and family education is a must.

Panic disorder and agoraphobia – Panic attacks are discrete episodes of paroxysmal severe anxiety and are characterized by severe and frightening autonomic symptoms (e.g. shortness of breath, palpitations, excessive perspiration), dizziness, faintness and chest pain – many patients believe they are in imminent danger of death or collapse and seek urgent medical attention. Panic disorder can occur with or without *agoraphobia*.

TYPICAL FEATURES OF PANIC ATTACKS

- Sudden onset
- Short duration (typically a few minutes)
- Rapidly escalating physical and psychological symptoms

Table 14: Classification of anxiety features

Psychological
• Fear and apprehension
• Inner tension and restlessness
• Irritability
• Impaired ability to concentrate
• Increased startle response
• Increased sensitivity to physical sensations
• Disturbed sleep
Physical
• Increased muscle tension
• Tremor
• Sweating
• Palpitations
• Chest tightness and discomfort
• Shortness of breath
• Dry mouth
• Difficulty swallowing
• Diarrhoea
• Frequency of micturition
• Loss of sexual interest
• Dizziness
• Numbness and tingling
• Faintness

- Incapacitating symptoms of breathlessness and/or palpitations
- Fear of impending death, collapse or loss of control
- Rapid escape (if possible) from situation where attack occurred
- Sometimes panic attacks are labelled nocturnal when they occur at night only.

'Co-morbidity' is common in individuals suffering from panic attacks or panic disorder. Compared with those with 'pure' panic disorder, patients with co-morbid panic and depression are more severely ill, more functionally impaired at home and at work.

DIAGNOSTIC GUIDELINES FOR PANIC DISORDER

- The individual experiences recurrent panic attacks that are not consistently associated with specific situation or object and that often occur spontaneously; these attacks are not associated with marked exertion or exposure to dangerous or life-threatening situations.
- A panic attack is characterized by all of the following:
  - A discrete episode of intense fear or discomfort
  - Starts abruptly
  - Reaches maximum intensity within a few minutes
  - Lasts at least several minutes
  - At least four symptoms are present (including at least one autonomic symptom)
  - The attack is not caused by a physical disease, an organic mental disorder, or another condition such as schizophrenia, mood disorder or somatoform disorder.

Table 15: Common features of generalized anxiety disorder

• Apprehension – Worries about future misfortune – Inner tension – Difficulty in concentrating
• Motor tension – Restlessness – Tremor – Headache
• Autonomic anxiety – Excessive perspiration – Dry mouth – Epigastric discomfort – Muscle tension and pain/stiffness

MANAGEMENT

a. *Psychological* – Helping patients to understand that their symptoms are not caused by serious physical ailment. Relaxation training can be helpful, but severely ill patients are more likely to benefit from cognitive behaviour therapy. Exposure therapy can be performed under supervision of a behaviour therapist.

b *Drugs* – High dose benzodiazepines (e.g. alprazolam) are effective but can cause substantial depression and should be prescribed in severely ill patients who have not responded to other treatment approaches. The antidepressant drugs (imipramine, clomipramine and selective serotonin re-uptake inhibitors (e.g. Paroxetine) are as efficacious in reducing anxiety symptoms, lessening agoraphobia and minimizing overall impairment.

Specific (isolated) phobias – Characteristic feature is a single, discrete fear of an object (e.g. a particular animal), a situation (e.g. flying) or an individual (e.g. a dentist). This fear causes significant emotional distress, and is often accompanied by marked avoidance.

Management – Behaviour therapy. Patients with a specific fear of blood or bodily injury tend to develop bradycardia and hypotension, and require tension exercises in addition to exposure therapy. Relaxation therapy may be useful. This may be coupled with behaviour therapy methods like systematic desensitization, exposure methods and modelling or flooding and implosion.

Social phobia (Social anxiety disorder) – Characteristic feature is an intense and persistent fear of being scrutinized or evaluated by others. The feared situations may be relatively discrete (e.g. public speaking) or diffuse. The disorder is more common in women and highest in those from low socioeconomic status.

Diagnostic guidelines for social phobia

- Marked fear of being the focus of attention, or fear of behaving in a manner that will be embarrassing or humiliating.
- Marked avoidance of fear situations
- Anxiety symptoms are restricted to, or predominate in, feared situations or are a contemplation of these
- In addition to more typical anxiety symptoms, at least one of the following is present:
  - Blushing or shaking
  - Fear of vomiting
  - Urgency or fear of micturition or defecation
- The symptoms cause significant emotional distress.

Agoraphobia – can occur as an isolated condition (or with panic attack) in which the individual experiences anxiety about being in places or situations from which escape might be difficult or embarrassing. Typical fears include being outside the home, being in a crowd, standing in a queue and using public transport. These feared situations are avoided or endured with marked distress, which is often lessened by the presence of a trusted friend involving almost all social situations outside the family circle ('generalized' subtype).

Table 16: Panic disorders

	Social phobia	*Panic disorder*
Panic attacks	Restricted to feared social situations	Occur unexpectedly in social encounters and when alone
Types of fear	Appearing foolish or awkward	Losing control or death
Company	Enjoy social encounters when accompanied by a trusted friend	Presence of a friend makes little difference

Differential diagnosis – The generalized subtype can be confused with panic disorder (Table 16).

Management – (a) β-blockers in management of performance anxiety. (b) Monoamine oxidase inhibitors, moclobemide and several selective serotonin re-uptake inhibitors like sertraline and paroxetine have been found efficacious. (c) Cognitive behaviour therapy (individually or in groups) is useful.

Obsessive-Compulsive Disorder (OCD)

A disorder in which there is persistent intrusion of unwanted thoughts, urges or actions that the patient is unable to stop.

Aetiology – OCD is widely accepted to result from genetic vulnerability and/or chemical changes in some areas of the brain. The precise pathogenesis is not completely understood.

Neurobiology – OCD patients have shown abnormalities in orbitofrontal cortex, cingulate cortex and caudate nucleus. In some children and adolescents, OCD develops after β-hemolytic streptococcal infection, an autoimmune reaction similar to that of rheumatic fever.

Genetic factors – Twin studies show concordance rates as high as 87% in monozygous twins compared with 47% in dizygous pairs.

Psychological theories – In cognitive behavioural theory, obsessions are considered anxiogenic. OCD patients cannot escape this anxiety and therefore develop compulsion in an attempt to reduce or prevent the feared consequences. Reduction of anxiety reinforces the compulsive behaviour.

Clinical features – Symptoms can arise acutely or insidiously.

Obsessions are frequent and persistent thoughts, impulses or images that are normally experienced as intrusive and senseless. They are usually accompanied by marked anxiety. Common obsessional themes are contamination, aggression, and sexual or religious ruminations.

Compulsions are repetitive behaviours, e.g. hand washing, checking, ordering or mental acts (e.g. counting, repeating words silently). It may involve repeating acts for a fixed number of times.

DIAGNOSTIC CRITERIA FOR OCD

- Obsessional thoughts, compulsive acts or both should be present on most days for at least 2 weeks
- They are recognized by patients as their own

- Patients have tried to resist unsuccessfully at least one obsessive thought or compulsive act
- The thoughts and acts are not pleasurable
- The thoughts, images, impulses and acts are unpleasantly repetitive

DIFFERENTIAL DIAGNOSIS

Anankastic (obsessive-compulsive) personality is often confused with OCD. Excessive cleanliness, checking and orderliness are not uncommon among healthy individuals, but they do not interfere with normal functioning.

Other anxiety disorders – Such as phobic disorders, generalized anxiety disorder and post-traumatic stress disorders have some features common with OCD.

Depressive disorder – Depression and OCD often occur together. In many patients OCD must be treated to alleviate depression.

Psychotic disorder particularly schizophrenia. It is necessary to differentiate obsession from thought insertion, which is an important feature of schizophrenia.

Tic disorders – Features of OCD are present in many patients with Tourette's disorder, and incidence of tics is greater in OCD.

Anorexia nervosa – has many features in common with OCD, but obsessive behaviour is limited to achieving weight loss.

Other disorders – such as body dysmorphic disorder and impulse control disorders (e.g. trichotillomania, kleptomania, pathological gambling) are (with tics and anorexia nervosa) considered by some to be OCD-spectrum disorders.

Brain damage, learning disabilities and autism may be associated with development of obsessions and rituals.

MANAGEMENT

a. ***Selective serotonin re-uptake inhibitors or tricyclic drugs.***
b. ***Cognitive behaviour therapy*** – The main approach in OCD is graded exposure and self-imposed response prevention. This requires patients to face their feared obsessions without 'undoing' them with their compulsions. Exposure should be of sufficient duration to be effective. An effective method known as thought stopping may also be used.

Drug treatment – Clomipramine 150–300 mg/d. SSRIs are effective in both OCD and depression, but must be given in higher doses, e.g. fluoxetine or paroxetine 60 mg/day.

Combined therapy – Combination of cognitive behaviour therapy and medication can be more effective than either alone.

Psychosurgery – is reserved for patients with severe illness that has not responded to multiple therapies. Selective operations separating areas of frontal cortex from deep limbic structures (e.g. cingulotomy, capsulotomy) can lead to improvement in 25–30% of such patients. ECT may be used in resistant cases.

Post-traumatic Stress Disorder (PTSD) and Acute Stress Disorder (ASR)

PTSD is a common, potentially disabling condition that affects all age groups and may have a lifelong, relapsing course if untreated.

Prevalence – Of individuals who experience combat disasters or personal tragedy (e.g. torture, accidents, abuse, rape) 30–35% suffer PTSD.

Vulnerability – Predisposing factors can be past history of psychiatric disorder, a 'neurotic' anxiety prone personality, exposure to previous traumatic experiences (including childhood abuse). Women are more likely to develop PTSD following interpersonal violence.

Co-morbidity – 'Pure' PTSD syndrome is uncommon, the condition is often complicated by concurrent affective disorder (particularly major depression, generalized anxiety and panic disorder), and by alcohol and drug abuse.

Behavioural effects – Dysfunctional behaviour is common in patients with PTSD and may be the presenting feature. Occupational instability, antisocial behaviour are also common. Those with PTSD are also likely to make negative life-course decisions.

Biology of PTSD – Abnormalities of the hypothalamo-pituitary-adrenal axis have been reported, these include hypocortisolaemia, and enhanced adrenocorticoid sensitivity to the effects of dexamethasone suppression ('super-suppression'), which is proportional to the clinical severity of PTSD. This suggests that the sensitivity of central glucocorticoid receptors is increased in PTSD, and distinguishes PTSD from other psychiatric disorders.

Other neurochemical findings include evidence of increased central catecholamine activity. High-resolution MRI reveals reduced hippocampal volume.

Functional neuroimaging studies have shown similarities between PTSD and OCD that distinguishes these conditions from other neurotic disorders. In both single-photon emission tomography reveals significant abnormalities of regional blood flow, predominantly affecting the basal ganglia and orbitofrontal cortex. These findings suggest that PTSD and OCD may have a common pathophysiology.

DIAGNOSTIC CRITERIA FOR POST-TRAUMATIC STRESS DISORDER

- A life-threatening event outside normal human experience
- Re-experiencing the trauma
  - Intrusive memories
  - Dreams or nightmares
  - Flashbacks with a sense of relieving the event
  - Distress at exposure to events resembling the trauma
- Avoidance of stimuli associated with the trauma
- Evidence of increased arousal
  - Sleep disturbances
  - Irritability
  - Hypervigilance
  - Exaggerated startle response
- Duration >1 month

Prevention – (a) *Primary prevention* includes preparing those at risk of experiencing trauma (e.g. emergency service workers, soldiers). Stress-inoculation programmes are used to prepare high-risk occupational groups for trauma. (b) *Secondary prevention* – Measures to reduce long-term psychiatric morbidity following trauma include counselling, of which 'critical incident' and 'psychological debriefing' are the most widely used.

Management

Psychological therapies – Cognitive techniques and exposure-based behavioural interventions are effective. In audiotape desensitization, the patient writes a detailed description of trauma (including feeling, sights, sounds and smells) which is recorded on to audiotape. Repeated listening to the audiotape reduces symptoms of hyperarousal within 2–3 weeks.

Drugs – are most effective following acute PTSD. Drugs acting on central serotonergic transmission have the most beneficial effect e.g. tricyclic antidepressants (e.g. imipramine), monoamine oxidase inhibitors (e.g. phenelzine) and SSRIs (e.g. fluoxetine). Generally drugs are given in higher doses and for longer duration than in the treatment of depression.

SOMATOFORM AND DISSOCIATION DISORDERS

Types of Hysterical Disorders

1. ***Conversion disorder*** – (Hysterical neurosis, conversion type). Here the special senses or voluntary nervous system are affected causing symptoms such as blindness, deafness, paralysis, akinesias, etc. for which there is no organic basis. Often the patient shows an inappropriate lack of concern ("la belle" indifference) about those symptoms which may actually provide secondary gains by winning sympathy. There is often a presentation with symptoms that are unexplained medically or physiologically.
2. ***Dissociative disorder*** – (Hysterical neurosis, dissociative type). Here alterations may occur in the patient's state of consciousness or in his identity to produce such symptoms as amnesia, somnambulism, fugue and multiple personality.

Aetiology

There is sufficient evidence to suggest that the symptoms are psychogenic and that the environmental factors are the important etiological factors.

1. *Age* – The peak incidence is between the ages of 20 to 35 years.
2. *Sex* – Incidence is higher in females.
3. *Intelligence* – People with low intelligence are more likely to develop this disorder.
4. *Personality* – Commonest is histrionic personality (characteristics – dramatizing and exhibitionistic, attention seeking, immature, having shallow and superficial emotional relationships).
5. *Marital status* – More common in unmarried, widows and divorcees.
6. *Sociocultural factors* – More common in primitive, developing and less sophisticated or cultured societies.
7. *Psychoanalytical theories* – Hysterical symptoms are viewed as symbolic representations and distorted expressions of unresolved intrapsychic conflicts about one's sexual drive (libido). When the libidinal energy manifests itself as somatic symptoms through the ego-defence mechanism of conversion, the resulting disorder is known as conversion disorder. When the libidinal energy manifests as psychological symptoms through the defence mechanism of dissociation, the resulting disorder is labelled dissociative disorder.

Clinical Manifestations

1. **Symptoms of conversion disorder** – These arise because of the involvement of voluntary neuromuscular system.
   a. *Motor symptoms* – These are of two types: (i) *Akinesia,* e.g. paresis or paralysis involving a part of the body like monoplegia, hemiplegia, paraplegia, etc. (ii) *Hyperkinesia* and dyskinesia, e.g. tremors, torticollis, convulsions or fits.

b. *Sensory symptoms* – These can be in the form of anaesthesia, hypoaesthesia, hyperaesthesia and paraesthesia. This disturbance can affect all the general sensations. Special organs of sense, like those for sight, hearing, smell and taste can also be disturbed resulting in blindness, deafness, etc.

c. *Visceral symptoms* – Common ones are hiccoughs, vomiting, dyspnoea, dysphagia, aphonia, etc.

2. **Symptoms of dissociation disorder –**

a. Somnambulism and somniloquy.

b. Amnesia – usually circumscribed and covers up the psychologically traumatic event.

c. Trance – An altered state of consciousness lasting for a few minutes to a few hours, during which the patient appears to be oblivious of the surroundings.

d. Fugue – An altered state of consciousness wherein the patient travels long distances over a period of days and subsequently has amnesia for the entire episode.

e. Multiple personalities like those of Dr Jekyl and Mr Hyde.

f. Ganser's syndrome, a rare disorder characterised by giving of "approximate answers", somatic or psychological hysterical symptoms, hallucinations and an apparent clouding of consciousness. Possession states where the soul of God or Goddess enters into one's body commonly seen in rural India during religious festivals.

Characteristics of Hysterical Symptoms

- Absence of organic basis for symptoms.
- They serve both primary gain (resolution of intrapsychic conflicts) and secondary gain (obtaining sympathy and attention).
- In conversion disorder –

Symptoms seldom occur when patient is alone, on the other hand, symptoms are exaggerated in presence of other persons. Patient is often indifferent to the symptoms even though they may appear to be incapacitating (la belle indifference). There is a stressful factor or event that will trigger or maintain symptoms. Symptoms change in quality and severity over a period of time.

Prognosis is determined by the following factors: 1. Intelligence – low intelligence usually associated with relapses. 2. Associated physical defects and physical illnesses – presence of these carries poor prognosis. 3. Personality – Histrionic personality does not carry a good prognosis. Even with adequate treatment, relapses are more frequent. 4. Possibility of environmental change – change in the environment relieves stress, ameliorates symptoms and ensures long lasting recovery.

Management

1. *Isolation of the patient* – from the pathogenic environment is very necessary in the acute attack. The patient may have to be hospitalized and no visitors be allowed to meet the patient.
2. *Placebo therapy* – sometimes help in relieving the symptoms because these patients are very suggestible.
3. *Drugs* – Anxiolytics, as in treatment of anxiety disorders, orally or parenterally help in some resistant cases by: (i) reducing secondary gain and (ii) by relieving stress.
4. *Narcoanalysis* – using subanaesthetic doses of sodium pentothal may be beneficial in some cases by providing an opportunity to the patients to discharge emotional conflicts.
5. *Hypnosis* – helps in relieving the symptoms by its value of suggestibility.
6. *Psychotherapy* – Supportive psychotherapy gives good results in most cases. Deep, analytical psychotherapy may benefit few patients. Family or marital therapy may be useful to correct associated maladjustments in family and marital units respectively.
7. *Relaxation therapy.*

SOMATOFORM DISORDERS

Somatization Disorder

A chronic syndrome characterised by multiple somatic symptoms for which no organic cause can be found and associated with psychological distress and persistent medical help-seeking. There are patients who have medically explainable symptoms but all investigations reveal no abnormality.

Aetiology – (a) *Age of onset* – before 30 years. (b) *Sex* – Much more common in women. (c) *Social status* – More common among the poor, uneducated and poorly employed persons. (d) *Family history* – More common in relatives of somatization disorder patients. (e) *Sociocultural factors* – Parental attitudes and teaching, cultural and ethnic traditions could be the reasons why some individuals 'learn' to somatise.

Clinical Features

1. Long history of multiple somatic complaints and long complicated medical histories.

2. Symptoms usually referable to any organ symptoms of the body but, nausea (or vomiting), pain in the extremities, shortness of breath in absence of exertion, amnesia, difficulty in swallowing, painful menstruation and burning sensation in sexual organs or rectum are among the most common symptoms.
3. Interpersonal problems and emotional distress. Anxiety, depression and strong suicidal ideation are common.
4. Patients tend to be exhibitionistic, self-centred, attention-seeking and manipulative. They tend to describe their symptoms in a dramatic and exaggerated manner. It is a bodily expression of inner psychological pain or stress. (Refer to conversion disorder).

Management – Optimum management depends on identifying psychosocial and physical symptoms early in the evolution of the disease.

Simple reassurance is sufficient in some patients when symptoms occur in the context of anxiety or depressive illness. However, a relevant explanation is preferable to bland reassurance.

A Technique Called 'Reattribution' is Useful

1. Make the patient feel understood by drawing on findings at assessment, and by acceptance and interest
2. Broaden the agenda to involve discussion of previously elicited psychological and social factors
3. Make the link between symptoms and psychological problems, using the following techniques:
   - Link to anxiety (e.g. overbreathing causing muscular tension and chest pain)
   - Demonstrate generation of symptoms (e.g. muscular pain from sustained contraction)
   - Link to life events
   - Link to another key individual's symptoms (e.g. response of his/her mother to stress).

Factitious disorders – These are characterized by physical or psychological symptoms that are feigned to assume a 'sick role'. Most patients are women, and more than half of them work in medically related occupations.

Munchhausen syndrome is an uncommon, dangerous subtype of factitious illness characterised by lying, deliberate use of self-induced symptoms to gain hospitalization, and admission to numerous hospitals.

Differential. diagnosis – (a) Malingerers produce symptoms to achieve a goal (e.g. to avoid court proceedings). The motivation of factitious disorder is obscure. (b) Somatoform disorders – Symptoms or signs with no organic explanation, but not produced deliberately. Patients with factitious disorder know they are producing symptoms, though they are unclear about their motives.

PAIN DISORDER

The disorder is similar to somatization disorder but here the predominant symptom is severe and prolonged pain for which there is no medical explanation.

Aetiology – (a) *Age* – More common between 30–50 years. (b) *Sex* – More common in females (c) *Occupation* – Manual and blue-collar workers are more prone. (d) *Family history* – Familial tendency. (e) *Psychoanalytical theories* – Pain is seen as a symbolic method of obtaining love, a punishment for wrong doing or atoning for one's guilt. (f) *Learning theories* – Pain is a learned response especially when pain is regarded or reinforced in some way. For example pain may become more intense when following increased attention by others, monetary benefits or by the successful avoidance of unpleasant activities.

Clinical features – (a) Severe and continuous pain of at least six months duration, which completely preoccupies the patient. (b) No organic basis for pain on physical examination. (c) In presence of related organic pathology, pain or the resulting impairment in functioning is grossly in excess of what could be expected from physical findings. (d) Long history of medical and surgical consultations and history of multiple and varied range of medications.

Management – 1. Supportive psychotherapy the objective being to rehabilitate the patient. 2. Drugs – Tricyclic antidepressants and selective serotonin re-uptake inhibitors, as in treatment of depressive disorders are effective in some cases.

HYPOCHONDRIASIS

A disorder characterised by an excessive concern about being afflicted with a disease and by a preoccupation with one's health.

Aetiology – (a) *Age* – More common in 30–50 age group although all age groups can be affected. (b) *Sex* – Equal incidence. (c) *Family history* – More common in relatives of patients with hypochondriasis. (d) *Psychoanalytical theories* – Aggressive and hostile impulses towards other people are transferred into physical complaints. The latter are viewed as a defence against guilt or expression of low self-esteem. (e) *Sociocultural factors* – Hypochondriasis is seen as an admission of the sick role made by a person who is facing an apparently insurmountable situation. The sick role offers an excuse for the patient to avoid unpleasant obligation and postpone onerous duties.

Clinical features – 1. Unrealistic interpretation of symptoms and sensations leading to a preoccupation with the fear of suffering from a serious disease. 2. Physical examination does not reveal any organic basis for the physical symptoms. 3. Persistence of the fear that one has a serious illness in spite of medical reassurance. 4. Anxiety and depression may accompany hypochondrial symptoms. 5. Symptoms are of at least 6 month's duration and involve multiple organ systems.

Management – 1. Supportive psychotherapy (to provide emotional support to patient and offer reassurance). 2. Treatment of accompanying anxiety or depression with anxiolytics and antidepressants respectively.

7. ANTIPSYCHOTIC DRUGS

Antipsychotic drugs – are now classified as 'typical' and 'atypical' (Table 17).

Typical antipsychotic effects are thought to be mediated by post-synaptic blockade of dopamine (D_2) receptors in the mesolimbic area of the brain.

Atypical antipsychotics can be divided into three groups.

Table 17: Antipsychotic drugs

Antipsychotic	*Chemical group*	*Dose (mg/ day p.o.)*
A. Typical		
Chlorpromazine		25–100
Thioridazine	Phenothiazine	25–600
Trifluoperazine		10–50
Haloperidol	Butyrophenone	1–20
Flupenthixol	Thioxanthene	3–18
Sulpiride	Substituted benzamide	400–2000
Pimozide	Diphenylbutyl piperidine	2–8
B. Atypical		
Risperidone		2–16
Iloperidone		2–12
Quetiapine		25–800
Olanzapine		5–20
Amisulpride		400–1200
Ziprasidone		20–50
Amisulpride		10–15
Clozapine		25–900

ANTIPSYCHOTICS

Depot Injections

1. Risperidone (Risperdal): 25–37.5 mg IM every 2 weeks
2. Fluphenazine decanoate: 12.5–25 mg IM every 2–4 weeks
3. Zuclopenthixol: 200–400 mg IM every 2–4 weeks
4. Flupenthixol: 20–40 mg IM every 2–4 weeks
5. Haloperidol decanoate: 50 mg IM every 4 weeks

Note: Clinically, 'atypical' simply refers to drugs with fewer or no side effects.

Therapeutic use – With the exception of clozapine, there are no major differences between typical and atypical antipsychotics in primary efficacy against the positive symptoms of schizophrenia. Atypicals may be more effective against negative symptoms, which are characteristically less amenable to treatment. Well-tolerated atypical antipsychotics must be used as a first-line treatment to improve compliance. Use of clozapine is restricted to schizophrenia unresponsive to or intolerance of conventional antipsychotics, because of the potential fatal side-effect of agranulocytosis. It is the treatment of choice for treatment resistant schizophrenia.

Contraindications – For typical antipsychotics cautions include cardiovascular, renal and liver disease, glaucoma and Parkinson's disease and epilepsy. Atypical drugs are contraindicated in pregnant and breastfeeding women.

Side effects

Typical antipsychotics

- Extrapyramidal side effects caused by nigrostriatal D_2 receptor blockade (e.g. acute dystonia, akathisia, parkinsonism)
- Tardive dyskinesia following prolonged use
- Anticholinergic effects (dry mouth, blurred vision, urinary hesitancy or retention, constipation)
- Anti-adrenergic effects (e.g. postural hypotension, inhibition of ejaculation)
- Sedation as a result of D_2, H_1 and α-receptor antagonism
- Cardiovascular effects: Tachycardia, arrhythmias, myocarditis, widening of QRS complex and prolonged QT interval
- Hyperprolactinaemia due to hypothalamo-pituitary D_2 receptor blockade causes amenorrhoea and galactorrhoea
- Skin and eye: Allergic and phototoxic skin reactions; long term use may cause skin pigmentation and corneal and lens deposits

- Haematological: Leucopenia, agranulocytosis
- Hepatic: Cholestatic jaundice, minor abnormalities of LFTs
- Neuroleptic malignant syndrome: A rare idiosyncratic reaction characterised by hyperthermia, muscular rigidity, autonomic instability, alteration in level of consciousness and elevated serum creatine phosphokinase (CPK)
- Others: Weight gain, hypothermia, agitation, anxiety, nausea.

Atypical antipsychotics

Clozapine: Sedation, hypersalivation, anticholinergic effects, weight. gain, postural hypotension. Agranulocytosis. Lowered seizure threshold. Myocarditis in rare cases.

Olanzapine: weight gain, sedation, dizziness, anticholinergic effects

Risperidone and Amisulpride: Insomnia, anxiety, agitation.

8. PSYCHOLOGICAL FACTORS AFFECTING MEDICAL CONDITIONS

PSYCHOSOMATIC DISORDERS

Disorders characterised by the manifestation of physical or somatic symptoms which are thought to be caused by emotional factors. The symptoms are referable to dysfunction of a single organ system which is under autonomic nervous system innervation. In this respect, psychophysiological disorders differ from conversion disorders in which the primary involvement is of the voluntary neuromuscular system. There are problems when there is an underlying pathology and medical disorder chest is exacerbated or relieved by psychological factors, e.g. an attack of bronchial asthma before an examination.

Clinical Manifestations

The commonly recognised psychosomatic conditions classified according to the organ system involved are:

1. *Gastrointestinal* – Peptic ulcer, ulcerative colitis, anorexia nervosa, irritable bowel syndrome.
2. *Cardiovascular* – Hypertension, myocardial infarction.
3. *Respiratory* – Bronchial asthma.
4. *Urogenital* – Menstrual disorders like amenorrhoea, dysmenorrhoea, menorrhagia, metropathia haemorrhagica.
5. *Dermatological* – Urticaria, hyperhidrosis, psoriasis, neurodermatitis, rosacea.
6. *Endocrinal* – Thyrotoxicosis, diabetes.
7. *Musculoskeletal* – Rheumatoid arthritis, tension headache.
8. *Vasomotor* – Migraine.

Etiological theories – Emotional disturbances could be responsible as predisposing, precipitating and perpetuating factors in these illnesses.

1. *Neuroendocrinal theory* – Based on the role played by the autonomic nervous system. The autonomic nervous system influences and is influenced by both, other parts of the nervous system like the limbic system, the neocortex, etc. and the endocrine glands like the anterior pituitary, the adrenal cortex, the adrenal medulla, etc. Complex inter-relationships of these various structures have been postulated to explain the translation of the conflicts arising from the problems of every day living into abnormal physiological functions and the tissue damage. The hypothalamus being the centre for the sympathetic and the parasympathetic activities is of central importance in these feedback circuits. Emotional disturbances acting through the hypothalamus affect the sympathetic and the parasympathetic systems, resulting in alterations in the functions of the viscera which these systems innervate. The end result of all these chain reactions would be the "devitalisation" of the organ, a process which would render the organ more susceptible to external or internal stimuli, both physical and physiological.
2. *Psychoanalytical theory* – The basic underlying defect is weakness of the ego, which is that aspect of the self which helps an individual to face realities of life. The development of both the ego and the personality of the individual takes shape mainly during the first few years of life. The future patterns of behaviour are laid down during these formative years. It has been suggested that in individuals who suffer from psychosomatic disorders, certain 'infantile residues' persist in later years. Whenever such individuals are faced with stresses of later life which they cannot cope with adequately, there occurs a psychological and/or physiological regression to these infantile or immature patterns of functioning resulting in the development of psychosomatic illnesses.

It must be borne in mind that psychological factors are not the only responsible agents but genetic, constitutional, endocrinal and metabolic disturbances also contribute to the development of these conditions. In an individual case, one or more of these factors may be of greater importance than the others. It is the complex interactions of all

these varied etiological factors which result in a psychosomatic condition. This view has a very important bearing in the treatment procedures of these diseases.

Management – Psychiatric treatment of the underlying emotional and personality factors may necessitate the use of psychotropic drugs, psychotherapy, behaviour therapy, biofeedback, etc. Treatment of the organic dysfunction by appropriate methods should be undertaken concurrently.

9. PERSONALITY DISORDERS

The presence of certain personality traits makes some individuals more vulnerable to develop behavioural abnormalities when faced with stressful events. With this degree of vulnerability, abnormal behaviour occurs only in response to environmental stress. In certain other personalities, unusual behaviour occurs even in the absence of stressful events. The latter group is referred to as personality disorders. *See* Table 18 for various personality disorders.

Table 18: Personality disorders (PD) clusters

1. Cluster-A (odd and eccentric)
– Paranoid PD
– Schizoid PD
– Schizotypal PD
2. Cluster B (dramatic, emotional and erratic)
Personality disorders thought to be on a 'psychopathic continuum'
– Antisocial PD
– Histrionic PD
– Narcissistic PD
– Borderline PD
3. Cluster C (Anxious and fearful)
Personality disorders characterised by 'introversion'
– Avoidant PD
– Dependent PD
– Obsessive-compulsive PD
4. Others like Anxious Personality Disorder and Passive Aggressive Personality Disorder

Diagnostic guidelines for specific personality disorders

- Markedly disharmonious attitudes and behaviours, involving usually several areas of functioning, e.g. affectivity, arousal, impulse control, ways of perceiving and thinking, and style of relating to others.
- The abnormal behaviour pattern is enduring, of long standing, and not confined to episodes of mental illness.
- The abnormal behaviour pattern is pervasive and maladaptive to a broad range of personal and social situations.
- The above manifestations appear during childhood or adolescence and continue into adulthood.
- The disorder leads to considerable personal distress but may only become apparent late in its course.
- The disorder is usually, but not invariably, associated with significant problems in occupational and social performance.

SUBTYPES OF PERSONALITY DISORDERS

I. **Paranoid Personality Disorder.** Evidence of at least three of the traits and behaviours:
   1. Excessive sensitiveness to setbacks.
   2. Tendency to bear grudges persistently.
   3. Suspiciousness and pervasive tendency to distort experience by misconstruing neutral or friendly actions of others as hostile or contemptuous.
   4. Combative and tenacious sense of personal rights, out of keeping with the actual situation
   5. Recurrent suspicions without justification regarding sexual fidelity of spouse or sexual partner.
   6. Tendency to experience excessive self-importance, manifest in a persistent self-referential attitude.
   7. Preoccupation with unsubstantiated 'conspiratorial' explanation of events, both immediate to the patient and world at large.

Patient may get involved in litigation on small issues

Management – Individual psychotherapy and supportive psychotherapy along with symptom based pharmacotherapy.

II. **Schizoid Personality Disorder.** Evidence is usually required for presence of at least three of the traits or behaviours given in the clinical description:
   1. Few, if any activities, provide pleasure.
   2. Emotional coldness, detachment or flattened activity.
   3. Limited capacity to express either warm, tender feelings or anger towards others.
   4. Apparent indifference to either praise or criticism.
   5. Little interest in having sexual experiences with another person (taking age into consideration).
   6. Almost invariable preference for solitary activities
   7. Excessive preoccupation with fantasy and introspection.

8. Lack of close friends or confiding relationships (or having only one) and of desire for such relationships.
9. Marked insensitivity to prevailing social norms and conventions.

Feature of this disorder may overlap with paranoid and schizotypal personality disorders. Psychotic features are absent. It is more common in men, and has an early onset in childhood.

Management – (a) Individual psychotherapy. (b) Psychoanalysis. (c) Involvement in group psychotherapy at a later stage.

III. **Schizotypal Personality Disorder.** A disorder characterized by eccentric behaviour and anomalies of thinking and affect, which resemble those seen in schizophrenia. At least three or four of the following should be present continuously or episodically for a period of at least 2 years:

1. Inappropriate or constricted affect (the individual appears cold and aloof).
2. Behaviour or appearance that is odd, eccentric or peculiar.
3. Poor rapport with others and tendency for social withdrawal.
4. Odd beliefs or magical thinking, influencing behaviour and inconsistent with subcultural norms.
5. Suspiciousness and paranoid ideas.
6. Obsessive ruminations without inner resistance, often with dysmorphobic, sexual or aggressive contents.
7. Unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization or derealization.
8. Vague, circumstantial, metaphorical, over-elaborate or stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence.
9. Occasional transient quasi-psychotic episodes with intense illusions, auditory or others, and delusion-like ideas, usually occurring without external provocation.

It is more common in individuals related to schizophrenics and is believed to be part of the genetic 'spectrum' of schizophrenia. Its onset, evolution and course are usually those of a personality disorder, and it runs a chronic course.

Management – (a) Psychoanalysis. (b) Individual psychotherapy. (c) Drugs: Antipsychotics help in brief psychotic episodes. Response to treatment is usually poor.

IV. **Antisocial/Dissocial Personality Disorder.** For diagnosis clear evidence is required for at least three of the traits or behaviours given in the clinical description. The disorder is synonymous with psychopathy and sociopathy.

1. Callous concern for the feelings of others.
2. Gross and persistent attitude of irresponsibility and disregard for social norms, values and obligations.
3. Incapacity to maintain enduring relationships, though having no difficulty in establishing them.
4. Very low tolerance to frustration and a low threshold for discharge of aggression, including violence.
5. Incapacity to experience guilt and to profit from experience, particularly punishment.
6. Marked proneness to blame others, or to offer plausible rationalizations, for the behaviour that has brought the patient into conflict with society.

There is no clear *aetiology,* several genetic, environmental and biological factors are associated such as more than normal prevalence of antisocial personality disorder in father, presence of inconsistent and impulsive parents, presence of soft neurological signs, non-specific EEG changes, and presence of conduct and/or attention deficit disorder in childhood.

Management – (a) Individual psychotherapy. (b) Psychoanalysis. (c) Group psychotherapy and self-help groups. (d) Drugs are of little value.

V. **Histrionic Personality Disorder.** For diagnosis evidence is required for presence of at least three of the traits or behaviours given in clinical presentations:

1. Self-dramatization, theatricality, exaggerated expression of emotions.
2. Suggestibility, easily influenced by others or by circumstances.
3. Shallow and labile affectivity.
4. Continual seeking for excitement, appreciation by others, and activities in which the person is centre of attraction (*attention-seeking attitude*).
5. Inappropriate seductiveness in appearance or behaviour.
6. Overconcern with physical attractiveness.

Associated features may include egocentricity, continuous longing for appreciation, feelings that are easily hurt, and persistent manipulative behaviour to achieve own ends. Tantrums, anger outbursts are common. The disorder is more common in females. There is an attempt to look charming and seductive.

Management – Psychoanalysis and psychoanalytic psychotherapy is helpful in removal of few symptoms.

VI. **Narcissistic Personality Disorder** is characterized by:
1. Ideas of grandiosity and inflated sense of self-importance
2. Preoccupation with fantasies of unlimited success.
3. Attention seeking, dramatic behaviour, wants constant praise, and unable to face criticism.
4. Lack of empathy with others, with exploitative behaviour.
5. Shaky self-esteem, underlying sense of inferiority, easily depressed by minor events.

Management – Individual psychotherapy may help.

VII. **Borderline Disorder.** is a disorder in which there is a marked tendency to act impulsively without consideration of the consequences, together with affective instability.

Types:

Impulsive type – Emotional instability and lack of impulse control. Outbursts of violence or threatening behaviour common, particularly in response to criticism by others.

Borderline type – Emotional instability, in addition the patient's own self-image, aims, and internal preferences (including sexual) are often unclear and disturbed. Characteristics of borderline personality disorder:

1. Significant and persistent disturbance of identity of self, e.g. 'who am I'? Marked uncertainty about major issues in life.
2. Unstable and intense interpersonal relationship patterns.
3. Impulsivity
4. Unstable emotional responses, with rapid shifts. Anger outbursts may occur.
5. Chronic feelings of boredom or emptiness with inability to stay alone.
6. Deliberate self-harm is common in the form of self-mutilation, suicidal gestures or accident-proneness.

Borderline personality disorder includes ambulatory schizophrenia and pseudoneurotic schizophrenia, which were earlier thought to be subtypes of schizophrenia.

Management – (a) Psychoanalytic psychotherapy. (b) Supportive psychotherapy. (c) Drugs: Major depressive episode if it occurs needs antidepressants with or without ECT. When aggressive and impulsivity are prominent use of antipsychotics, lithium and carbamazepine.

VIII. **Anxious Avoidant Personality Disorder.** For diagnosis clear evidence of presence of at least three of the traits or behaviours given in clinical description:
1. Persistent and passive feeling of tension and apprehension.
2. Belief that one is socially inept, personally unappealing, or inferior to others.
3. Excessive preoccupation with being criticized or rejected in social situations.
4. Unwillingness to become involved with people unless certain of being liked.
5. Restrictions in lifestyle because of need to have physical security.
6. Avoidance of social or occupational activities that involve significant interpersonal contact because of fear of criticism, disapproval or rejection.

This disorder is an epitome of what is often called 'inferiority complex'. Secondary depression is common.

Management – (a) Individual psychotherapy. (b) Group psychotherapy. (c) Behaviour therapy in particular social skills and assertiveness training.

IX. **Dependant Personality Disorder.** For diagnosis clear evidence for presence of at least three of the traits or behaviours given in clinical description:
1. Encouraging or allowing others to make most of one's important life decisions.
2. Subordination of one's own needs to those of others on whom one is dependent, and undue compliance with their wishes.
3. Unwillingness to make even reasonable demands on people one depends on.
4. Feeling uncomfortable or helpless when alone, because of exaggerated fears of inability to care for oneself.
5. Preoccupation of being abandoned by a person with whom one has close relationship, and of being left to care for oneself.
6. Limited capacity to make everyday decisions without an excessive amount of advice and reassurance from others.

Associated features may include perceiving oneself as helpless, incompetent, and lacking stamina. There may be overlap with avoidant and passive-aggressive personality disorders. Some exhibit masochistic character.

Management – (a) Individual psychotherapy. (b) Group psychotherapy. (c) Behaviour therapy in the form of assertiveness training. Response to therapy is very good.

X. **Obsessive-Compulsive (Anankastic) Personality Disorder.** Diagnostic guidelines: Evidence required for presence of at least three of traits or behaviours given in clinical description:
1. Feeling of excessive doubts and caution.
2. Preoccupation with details, rules, lists, order, organization or schedule.
3. Perfectionism that interferes with task completion.

4. Excessive conscientiousness, scrupulousness and undue preoccupation with productivity to the exclusion of pleasure and interpersonal relationships.
5. Excessive pedantry and adherence to social conventions
6. Rigidity and stubbornness.
7. Unreasonable insistence by the patient that others submit to exactly his or her way of doing things, or unreasonable reluctance to allow others to do things.
8. Intrusion of insistent and unwelcome thoughts or impulses.

The disorder is more common in males. Major depressive episodes are common. Psychodynamically the disorder is believed to result from fixation at anal sadistic phase, with employment of 'reaction formation' as a defence mechanism.

Management – (a) Psychoanalysis. (b) Group therapy. (c) Medication as in OCD.

XI. **Passive-Aggressive Personality Disorder** is characterised by following clinical features:

1. Significant and persistent passive resistance to demand for adequate social and occupational performance.
2. Stubbornness, intentional inefficiency, procrastination, unjustified protests, forgetful and/or dawdling are used to achieve the purpose.

Passive resistance is viewed as expression of 'covert anger' or 'retroflexed anger'. This behaviour is often chosen in spite of the fact that a more direct and active way of showing an opinion and/or resisting was possible.

Management – (a) Supportive psychotherapy. (b) Behaviour therapy. (c) Group therapy. (d) Drugs: Antidepressants if secondary depression.

10. SEXUAL AND GENDER PERSONALITY DISORDERS

A. **Gender identity disorders**

1. **Transsexuality** – Some individuals feel so unhappy in the gender of their birth and so much 'in sympathy' with the opposite sex that they seek full gender reassignment, hoping they will be happy in their new sex.

Types

Primary transsexualism. Onset in childhood with a stable course over time. *Types:* Male-to-female, or female-to-male.

Secondary transsexualism. Onset later in life. This category includes effeminate homosexuals, transvestites who secondarily become transsexuals. *Treatment:* (a) Reconciliation with the anatomic sex by psychotherapy and behaviour therapy (e.g. aversion therapy) may help in secondary transsexuals. (b) Sex change to the desired gender by sex reassignment surgery.

Necessary routine before sex reassignment surgery

- Confirmation of primary, stable long-standing transsexualism
- Possibility of stress-induced transsexualism is considered and eliminated
- Psychotherapy for at least 6 months prior to surgery
- Experimental trial in the new gender role to assess patient's ability to adjust in the 'new role'

2. **Cross dressing** is GID if transient and stress-related. Some men dress in female garments to enhance their sexual arousal. Other men feel a compulsion to dress as a female, and describe a sense of relief, relaxation and well-being when they do so. This is termed '*transvestism'*.

Less commonly some females wear clothes of the opposite sex (*dual-role transvestism)* but without a desire for a permanent sex change and without any sexual excitement as is seen in fetishist cross-dressing.

Management – Psychiatric help may be sought if cross-dressing causes problems in the family relationship. In such cases, marital or family therapy can be helpful.

3. **Gender-identity disorder of childhood.** It is similar to transsexualism with age of onset between 2 and 4 years.

Clinical features

- Persistent and strong urge to be of the opposite gender
- Distress regarding the anatomic sex with strong denial of such sex (in contrast to transsexualism)
- Involvement in usual activities, sports and clothing style of the perceived gender
- Onset before puberty

Management – Similar to transsexualism. When anatomic sex and gender-identity are opposing, treatment is based on gender-identity of the individual. Supportive and psychodynamic psychotherapy are a must.

4. **Inter-sexuality.** Presence of gross anatomical or physiological aspects of the opposite sex. These can be in:
   - External genitals, e.g. pseudo-hermaphroditism
   - Gonads, e.g. ovotestes

- Internal sex organs, e.g. true hermaphrodite
- Hormonal disturbances, e.g. testicular feminization syndrome, congenital adrenal hypoplasia
- Chromosomes, e.g. Turner's syndrome, Klinefelter's syndrome
- CNS disorder, e.g. temporal lobe affection (rare)

B. **Psychological and behavioural disorders associated with sexual development and maturation.**

1. **Sexual maturation disorder.** Usually starts in adolescence with uncertainty about gender identity or sexual orientation (heterosexual, homosexual, or bisexual). This often leads to anxiety and depression.
2. **Ego dystonic sexual orientation.** The individual desires to change the orientation because of psychological symptoms or distress. The disorder is seen commonly in homosexuality.

Homosexuality is sexual relationship between individuals of the same sex. It is a disorder only when it is the predominant, significant and persistent mode of sexual relationship for that person and is dystonic (e.g. causes significant distress to the individual). Female homosexuals are labelled 'lesbians'.

Types of homosexual disorders

1. *Obligatory homosexuality*
   - Only homosexuality
   - No heterosexuality
2. *Preferred homosexuality*
   - Predominant homosexuality
   - Occasional heterosexuality
3. *Bisexuality:* Almost equal homo- and heterosexuality
4. *Situational homosexuality*
   - Predominant heterosexuality
   - Occasional homosexuality
5. *Latent homosexuality*
   - Only heterosexuality
   - Fantasies of homosexuality

Management – is offered under certain conditions:

a. Self-referral by a homosexual person for seeking a change in sexual orientation towards heterosexuality.

b. Self-referral for removal of distress associated with homosexuality but not for a change in sexual orientation.

c. Referral by parents, or relatives or others

For seeking a change in sexual orientation:

- (i) Psychoanalytical psychotherapy (especially when associated with neurotic symptoms or traits). (ii) Behaviour therapy: Aversion therapy, covert desensitization (especially if there is a phobia of heterosexual relationship). (iii) Supportive psychotherapy. (iv) Occasionally androgen therapy.
- *For seeking removal of distress only:* (i) Psychotherapy: Psychoanalysis and supportive depending on personality character. (ii) Drugs: Antidepressants and/or benzodiazepines for associated depression and anxiety.

d. *Referred by others.* Information regarding normal sexuality and homosexuality in detail leaving the ultimate decision of choosing the sexual orientation to the individuals. The person's motivation and presence of significant distress are important factors in therapy.

3. **Sexual relationship disorder.** The gender identity disorder of sexual preference leads to difficulties in establishing and/or maintaining sexual relationships. In this case both diagnoses are justified.

C. **Paraphilias (Disorders of sexual preference)** – Paraphilias are disorders in which sexual arousal occurs persistently and significantly in response to objects which are not connected with normal sexual arousal (e.g. non-human objects, suffering or humiliation of self and/or sexual partner, children or non-consenting person). Following are such disorders:

1. ***Fetishism (***Fetishism means magical). Here sexual arousal occurs either solely or predominantly with a non-living object, generally intimately associated with the human body such as shoes, underpants, bras, stockings, etc. It occurs exclusively in males and is often associated with masturbation.
2. ***Fetishistic transvestism*** occurs exclusively in hetero-sexual males. There is cross-dressing for sexual arousal. The disorder may be associated with fantasies of other males approaching the individual who wears a female dress. Masturbation or rarely coitus is associated with cross-dressing to achieve orgasm.
3. ***Sexual sadism.*** Here the sadist is sexually aroused by physical and/or psychological humiliation, suffering or injury of the sexual partner (the victim). Methods used range from restraining by tying, beating, burning, cutting, stabbing, to rape and even killing.
4. ***Sexual masochism*** is the reverse of sexual sadism. Here the person is sexually aroused by physical and/or psychological humiliation, suffering or injury inflicted on self by others (usually sadist). Most often the masochist is a female.

   Sexual sadism and sexual masochism are often seen in the same individual and are hence classified as *sadomasochism.*

5. ***Exhibitionism*** is a persistent or recurrent way of sexual arousal by exposure of one's (usually male) genitals to an unsuspecting stranger (usually female or child). This is followed by masturbation to achieve orgasm.
6. ***Voyeurism*** is a persistent or recurrent tendency almost always by male to watch unsuspecting individuals (usually of the opposite sex) naked, disrobing or engaged in sexual activity. This is followed by masturbation to achieve orgasm without the observed person being aware.
7. ***Frotteurism*** is a persistent or recurrent habit of touching or rubbing against an unsuspecting, nonconsenting person (usually of the opposite sex). It is often indulged in crowded places, e.g. trains or buses. This is often observed in adolescent males.
8. ***Paedophilia*** is a persistent or recurrent involvement of an adult in sexual activity with prepubertal children, either heterosexual or homosexual. This may be associated with sexual sadism. The paedophilic behaviour may be either limited to incest or spread outside the family.
9. ***Zoophilia*** (Beastility), a persistent involvement in sexual activity with animals is very rare. Occasional or situational zoophilia is more common.
10. ***Other paraphilias*** include sexual arousal with urine (urophilia), faeces (coprophilia), enemas (klismaphilia), corpses (necrophilia), etc.

Management – (a) *Psychoanalysis* helpful if patient is psychological minded and has good ego strength. (b) *Behaviour therapy*: Aversion therapy, treatment of choice in severe, distressing paraphilia. (c) *Drugs*: Antipsychotics for severe and dangerous aggression associated with paraphilias. Antiandrogens (e.g. medroxyprogesterone) in presence of excessive sexual activity. (d) Psychosurgery (amygdalotomy) occasionally in dangerous, aggressive sexual behaviour if persistent or recurrent.

D. Sexual problems

Sexual dysfunction can cause much distress for individuals and couples. It is necessary to take a clear and sensitive psychosexual history based on a knowledge of sexual physiology, and distinguish between problems involving loss of sexual desire, the arousal phase and orgasm.

Male problems

1. **Loss of libido**

Causes

- Hypogonadism
- Marital conflict
- Alcohol abuse
- Physical illness
- Depression
- Work stress and tiredness

2. **Erectile dysfunction** is an inability to achieve or maintain an erection, making intercourse difficult or impossible. The cause may be primary but is more often secondary, the incidence increases steeply with age.

Organic causes

- Vascular disease (most common cause of erectile dysfunction in middle-aged and elderly men)
- Neuropathy, e.g. diabetes mellitus, multiple sclerosis
- Abnormal veins draining the penis (can cause primary erectile failure)
- Nerve damage (through injury or pelvic surgery)
- Local penile deformities (e.g. Peyronie's disease)
- Tobacco, alcohol
- Drugs (e.g. β-blockers, thiazide diuretics, certain antidepressants, major tranquillizers, anticonvulsants, H_2-receptor blockers)

Psychological factors can cause, perpetuate and complicate erectile dysfunction. Performance anxiety due to life events, stress, organic factors or relationship factor leads to initial failure, doubt and worry followed by 'spectatoring' in which self-critical monitoring of the body's performance leads to repeated failure, such that the situation becomes chronic.

Management – Ideally, methods of treatment are recommended according to the predominant cause of the problem, but in clinical practice treatment depends largely on which method the man and his partner find most acceptable.

1. *Behavioural treatment* for the couple (e.g. Masters and Johnson's sensate focus therapy) is effective in treating performance anxiety, but are less successful when organic disease is present.
2. *Intracavernosal injections* of vasoactive drugs (e.g. papaverine, phentolamine) is effective in most patients other than those with severe vascular disease.
3. *Mechanical devices* (e.g. vacuum pumps with constriction rings) are simple to use and are effective in all types of erectile problem, but patients may find them intrusive and expensive.
4. *Oral medication* – Sildenafil, vardenafil and tadalafil are phosphodiesterase (PDES) inhibitors that selectively inhibit the breakdown of vasoactive substances in penile tissue, enhancing and prolonging the erectile response once the process of arousal has begun, but is less effective when severe physical causes (e.g. advanced diabetic neuropathy) are present.

Contraindications – (a) Those who have suffered myocardial infarction, stroke or life threatening arrhythmia during last 6 months. (b) Presence of cardiac failure or unstable angina. (c) Hypotension or hypertension. (d) Patients taking nitrates for angina. Dosage: Sildenafil 50 mg one hour before sexual activity tadalafil 10-20 mg. Based on effectiveness and tolerance dose can be increased to 100 mg or reduced to 25 mg. Most persons report only mild and transient side effects (e.g. facial flushing).

3. **Premature ejaculation** – is a problem when ejaculation regularly occurs before or within seconds of penetration.

Management – (a) Behavioural therapy programmes such as the 'stop-start' and 'squeeze' techniques teach ejaculatory control but depend on a cooperative sexual partner and involve masturbatory exercises that some men find unacceptable. These techniques require patience and motivation, and because these conditions can be difficult to meet, drug therapy may sometimes be considered. (b) Drugs: Some antidepressants (e.g. clomipramine, selective serotonin re-uptake inhibitors such as paroxetine and sertraline) have the side effect of delaying ejaculation. Although this effect does not last when the drug is discontinued, the resulting increase in confidence may be of benefit.

4. **Retarded or absent ejaculation** is less common and has several possible organic causes. However it may be caused entirely by psychological or emotional factors that are amenable to behaviour therapy, couple therapy or individual psychotherapy.

Female problems

1. **Loss of libido** (Frigidity) is characterized by loss of desire for sexual activity which is not secondary to other causes like premature ejaculation or dyspareunia. Contributory factors may include fear of pregnancy, unsatisfactory past sexual experiences, marital disharmony or fatigue.

Treatment – Hormone regimes using oestrogen and progesterone, singly or in combination, can restore feelings of general wellbeing in postmenopausal women, but are disappointing in established loss of libido. Loss of libido in women is also dependent on testosterone, which has been used successfully. Mechanism of action is unclear; it may act centrally via the hypothalamus, or peripherally by causing growth and enhanced sensitivity of the clitoris. There is a risk of side-effects (e.g. hirsutism), and not all women respond. Most women report reduced libido in later stages of pregnancy and while lactating, principally in response to high levels of prolactin. These high levels are temporary, but the problem can become chronic if complicating factors like postnatal depression are present.

2. **Dyspareunia**

Vaginismus is a spasm of the perianal muscles that circle the entrance to the vagina. It can be intensely painful and is often accompanied by phobic anxiety about vaginal penetration, which can lead to fears and panic when penetration is attempted. In *primary* cases, vaginismus can be associated with an excessively strict and negative upbringing regarding sex, or there may be history of sexual abuse as a child. The problem can also develop *secondarily* after sexual assault, clumsy vaginal examination, painful vaginal infection or complication of episiotomy. Sometimes there is no obvious cause.

Treatment – Most patients benefit from combined approach of supportive counselling and behaviour therapy, often with relaxation training and use of graded sizes of vaginal dilators; this allows the women to develop confidence and control of perineal muscles. Ideally, the women's sexual partner is involved in therapy from an early stage; by working with his partner, he can overcome any fear of hurting her. Other causes of dyspareunia include insufficient vaginal lubrication. It may result from insufficient or poor quality foreplay, or may be a side effect of drugs such as b-blockers.

3. **Anorgasmia:** Inability to experience orgasm may need education about importance of foreplay and the role of the clitoris in female sexual pleasure. Treatment programmes based on relaxation, masturbation training and enhancement of pleasure using fantasy are available for women with persistent difficulties.

Secondary anorgasmia may be caused by conflict within a relationship or by pelvic surgery.

11. PERINATAL PSYCHIATRY

Perinatal psychiatry deals with mental illnesses associated with childbearing. It is also concerned with associated psychiatric problems in fathers and the special needs of parents who are psychiatrically ill and have young children.

COMMON PSYCHOLOGICAL PROBLEMS FOLLOWING CHILDBIRTH

- Low mood
- Anxiety

- Tiredness
- Ambivalence about the baby
- Feelings of inadequacy
- Reduced or absent sexual interest
- Anger and bitterness

1. **Postnatal blues.** In first few days after childbirth, many women experience anxiety, lack of self-confidence, unpredictable mood swings, tearfulness, difficulty concentrating and a general feeling of confusion.
   Risk factors – History of premenstrual syndrome.
   Management. – Understanding, and support of professionals, family and friends. There is no indication for drug therapy in such a brief, self-limiting disorder.
2. **Puerperal psychosis** is an uncommon affective disorder akin to manic-depressive illness. There is pronounced disturbance of mood, which can be consistently low or high, or can fluctuate unpredictably between the two. Delusions and/or hallucinations are also present. It usually begins in the first week after delivery.

PREDISPOSING AND PRECIPITATING FACTORS

- Previous family history of psychosis, particularly puerperal
- First pregnancy
- Perinatal death
- Alcohol or drug abuse
- Poor marital relationship
- Poor social support

Management. – Antipsychotic and possibly antidepressant medication. In breastfeeding women, antipsychotic, e.g. haloperidol. Hospitalization is usually necessary.

3. **Postnatal depression** is the most common major complication (physical or psychiatric) of the postnatal period, with a peak after about 3–4 weeks. Many of the features occur in the normal puerperium. The mood is generally low, she may lose interest, feels hopeless, helpless, guilty or inadequate, has loss of appetite and difficulty sleeping. Many of these features occur in normal puerperium, but postnatal depression is differentiated by the pattern of symptoms and the severity and consistency with which they occur.

Management – Fluoxetine 20 mg, or if the woman is breastfeeding imipramine increased from 25 mg to 75 mg over a few days. Response occurs after 2 weeks.

Treatment should be continued for at least 3 months after remission. Good supportive and interpersonal psychotherapy.

12. SUBSTANCE USE DISORDERS

Many substances are taken to alter the mental state of the user. Such substances can be classified according to whether their major effect is to alter perception, or to stimulate or depress the CNS, though there is some overlap between groups.

ROUTES OF SUBSTANCE ABUSE

Ingestion is convenient, but absorption is relatively slow and the impact of the drug on the brain is correspondingly decreased, unless large quantities are taken. Drugs taken by ingestion to alter the mental state include anticholinergic drugs and plant preparations, benzodiazepines, clomethiazole, ethanol, opioid analgesics and sympathomimetics.

Inhalation allows more rapid absorption of cannabis, cocaine, nicotine, opiate analgesics, organic nitrites (e.g. isobutyl nitrite) and volatile substances. Volatile substances are usually 'bagged' (sprayed into a plastic bag and inhaled until the individual loses consciousness) or 'huffed' (sprayed into a cloth held to the mouth).

Absorption through mucous membrane ('snorting' or 'snuffing') is the method most commonly used with cocaine. The drug is stuffed into the nostrils, where it is absorbed.

Injection subcutaneously ('skin popping') or iv ('mainlining') is the fastest method of delivering drugs to the brain in high concentrations and is the route preferred for the more potent opioid analgesics.

HAZARDS OF ABUSE

- Because substance abuse is usually illegal, even seriously ill individuals may not be referred for immediate medical help and thus irreversible brain damage may result.
- Contaminants – Some complications result from deliberate addition of substances to dilute ('cut') the drug before it is sold. In other cases, preparation of the drug for injection (e.g. passage through cigarette filters, cotton wool) introduces contaminants. Particulate contaminants cause long-term progressive granulomatous pulmonary lesions.
- Other hazard include:
  - Infection with hepatitis B, C and D virus and HIV
  - Injection site abscess caused by infection or leakage of drug into the tissues

- Bacterial infection of veins and heart valves
- Candidiasis
- Inadvertent intra-arterial injection leading to digital gangrene

Body-packing is the practice of smuggling drugs in small packets (using condom, foil and cellophane) are swallowed for later retrieval from vomit or faeces, or are inserted into the vagina or rectum. Acute intestinal obstruction may result, and overdose is a hazard if a packet bursts.

TYPES OF DRUG USE DISORDERS

1. **Acute intoxication** is a transient condition following intake of alcohol or other psychoactive substance, resulting in disturbance in level of consciousness, cognition, perception, affect or behaviour, or other psychophysiological functions and responses.

   The intensity of intoxication decreases with time, and effects eventually disappear in absence of further use of the substance.

Indications to suggest any associated complications

- Uncomplicated (Symptoms of varying severity particularly at high dose levels)
- With trauma or other bodily injury
- With other medical complications (e.g. inhaled vomitus, hematemesis)
- With delirium
- With perpetual distortions
- With coma
- With convulsions, and
- Pathological intoxication (only with alcohol)

2. **Withdrawal state** – is characterized by a cluster of symptoms, mostly specific to the drug or substance used, which develop on total or partial withdrawal of the drug, usually lasts for few hours to few days. Withdrawal state is further divided into uncomplicated, with convulsions and with delirium.
3. **Dependence syndrome** is a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value.

   An important feature of dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs, tobacco or alcohol (Table 19).

Table 19: Drugs or substances likely to produce dependence

Drug or substance	*Route*
• Alcohol	Oral
• Opioids	Oral, parenteral, smoking
• Cannabis (marihuana)	Smoking, oral
• Cocaine	Inhalation, smoking
• Amphetamine	Oral, parenteral
• LSD	Oral
• Barbiturates, benzodiazepines	Oral, parenteral
• Volatile solvents	Inhalation
• Phencyclidine	Smoking, inhalation, oral, parenteral

DIAGNOSIS OF DEPENDENCE

At least three of the following have been experienced or exhibited at some time during the previous year:

- Strong desire or sense of compulsion to take the substance.
- Difficulties in controlling substance-taking behaviour in terms of its onset, termination or levels of use.
- A physiological withdrawal stage when substance use has stopped or reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms.
- Evidence of tolerance, such that increased doses of the psychoactive substance are required in order to achieve effects originally produced by lower doses (e.g. in opiate and alcohol dependent individuals).
- Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased duration to obtain or take the substance or to recover from its effects.
- Persisting with substance use despite clear evidence of overtly harmful consequences, e.g. liver injury from excessive drinking, depressive mood states from heavy substance use, or drug-related impairment of cognitive functioning.

Types of dependence: Dependence can be: (a) *Psychological:* Development or craving for a substance because its effects are perceived as pleasurable. (b) *Physical:* which implies occurrence of a physiological or biochemical change produced by drugs or substances which the body requires continuous presence of, if a withdrawal syndrome is to be avoided after discontinuation of the same.

4. **Harmful use** – Abuse is characterized by:
   - Continued drug use in spite of awareness of harmful medical and/or social effect of the drug being used, and/or
   - A pattern of physically hazardous use of drug (e.g. driving during intoxication).

ALCOHOL USE DISORDERS

Etiological explanations of alcohol dependence:

- Alcoholism is simply caused by drinking too much
- Alcoholism is a result of self-medication for life-stresses
- Alcoholism is caused by depravity of temperament
- Alcoholism is hereditary

Personality and psychological factors – Two types of alcoholism have been suggested:

- *Milieu-limited:* Later onset (after 25), less severe, only slight heritability, high avoidance, reward dependence
- *Male-limited:* Early onset, greater severity, associated with criminal behaviour, highly heritable, novelty-seeking may be an important determinant of substance abuse, rather than alcohol dependence, and this may be partly associated with genetic variants at the dopamine receptor 4 (DRD_4).

Hereditary factors. Most twin studies of alcohol dependence have demonstrated that the concordance rate is greater in monozygotic twins than in dizygotic twins, confirming that this clustering is partly caused by genetic factors. Adoption studies have indicated that sons of alcohol-dependent biological parents who are adopted by other families are at greater risk of developing the disorder.

Aldehyde dehydrogenase gene. One of the clearest demonstrations that a single gene can profoundly affect drinking behaviour and alcohol dependence is the 'protection' conferred by a variant of the gene responsible for alcohol metabolism in the liver. Following absorption, alcohol is metabolized to acetaldehyde by alcohol dehydrogenase. The toxic products (acetaldehyde) is then metabolized by aldehyde dehydrogenase 2 (ALDH2). If ALDH2 activity is inhibited, acetaldehyde accumulates and the individual experiences flushing, palpitations and nausea following ingestion of small quantities of alcohol. About 40% of Orientals carry an inactive variant of ALDH2 (the gene differs by a single base), which causes the adverse symptoms. Individuals carrying the gene for inactive ALDH2 are less likely to become alcohol dependent.

Other genetic markers. Other than the association of alcohol dependence and a genetic marker at the dopamine receptor 2 gene, two genome-wide scans using a genetic linkage approach in families have implicated several chromosomal regions in alcohol dependence. These include chromosome 11 close to the DRD_4 receptor and tyrosine hydroxylase genes, chromosome 4 and chromosomes 1 and 7.

ACUTE ALCOHOLIC INTOXICATION

Clinical features

CNS depression. Ethanol is a CNS depressant which, in small quantities interferes with cortical processes, and may in larger doses, depress medullary function. The effects of ethanol on CNS are generally proportional to blood ethanol concentration (Table 20).

Vasodilation. Ethanol is a peripheral vasodilator and may cause hypothermia and hypotension in severely intoxicated individuals.

Hypoglycemia. Inhibition of hepatic glucogenesis may result in hypoglycemia, particularly when poisoning follows fasting, exercise or chronic malnutrition. Typically alcohol-induced hypoglycemia occurs within 6–36 hours after ingestion of a moderate to large amount of alcohol.

Table 20: Features of acute alcoholic intoxication

Blood ethanol (mg/litre)	*Features*
<500	Talkativeness, subjective feeling of well-being
500–1000	Inebriation Slurred speech Emotional instability Incoordination Loss of sensory perception
1000–5000	Intoxication • Loss of sensory perception • Muscular incoordination • Ataxia, blurred or double vision • Coma • Convulsions
>5000	Very severe intoxication • Coma • Hyporeflexia • Hypothermia • Respiratory depression • Poor airway protection

Note: Habitual drinkers may have few symptoms, even at high blood concentrations, whereas inexperienced drinkers may be comatose at blood ethanol concentrations of 1000 mg/litre.

The patient is often comatose and hypothermic; the usual features of hypoglycemia (e.g. flushing, sweating, tachycardia are often absent).

Lactic acidosis. Usually mild is uncommon but potentially serious complication and occurs particularly in patients with severe liver disease, pancreatitis or sepsis.

Alcoholic ketoacidosis may develop in alcoholics who have recently taken to heavy drinking; it results from a combination of dehydration, glucopenia, increased lipolysis and ketogenesis. Onset of ketoacidosis is usually preceded by an ethanol-free interval with frequent vomiting; ethanol may be undetectable in blood.

Other features. While intoxicated, patient may have suffered an injury, for example to the head or a peripheral nerve. Amnesia is common, and a hangover often results in individuals not habituated to alcohol.

MANAGEMENT

Supportive measures particularly protection of airway. In more severe cases acid-base balance should be determined 2-hourly. Blood sugar hourly and rate of i.v. glucose adjusted accordingly.

Lactic acidosis – Correction of hypoglycemia, hypovolemia and circulatory insufficiency, if present but also infusion of sodium bicarbonate.

Alcoholic ketoacidosis is corrected by infusion of 5% glucose alone.

Haemodialysis if blood alcohol concentration exceeds 7500 mg/L and/or metabolic acidosis not easily corrected by above measures.

Naloxone and flumazenil may improve consciousness (even in patients who have not ingested an opiate or benzodiazepine with ethanol) but routine use is inappropriate.

CHRONIC ALCOHOLISM

See Table 21 for complications of alcohol dependence.

Withdrawal syndrome. Chronic alcohol consumption (alcohol dependence syndrome) results in the development of withdrawal symptoms when alcohol intake ceases.

Pathophysiology. Ethanol appears to act at the benzodiazepine g-aminobutyric acid (GABA) chloride receptor complex. On withdrawal from alcohol, the receptor complex is devoid of the potentiating effects of ethanol on chloride flux; there is a subsequent decrease in the efficacy of GABA, resulting in CNS 'disinhibition'.

Table 21: Complications of alcohol dependence

Physical
Gastrointestinal
• Periodontal disease and caries
• Oral infections, leukoplakia and malignancy
• Alcoholic gastritis and hematemesis
• Alcoholic enteropathy and malabsorption syndrome
• Colonic malignancy
Hepatobiliary and pancreatic
• Hepatomegaly: Fatty liver, alcoholic hepatitis and fibrosis
• Acute and chronic relapsing pancreatitis
• Malabsorption syndrome
• Overt expression of latent genetic hepatic porphyrias
Cardiovascular
• Cardiac arrhythmia
• Cardiomyopathy
• Hypertension
• Hypercholesterolemia
Neurological
• Giddiness, tremors
• Stroke
• Cerebral dementia, cerebellar degeneration
• Demyelinating syndrome – Central pontine myelinolysis, Marchiafava-Bignami syndrome
• Neuropathy: Sensory, motor, mixed, autonomic
• Nutritional deficiencies
• Wernicke-Korsakoff syndrome
• Pellagra
• Tobacco-alcohol amblyopia
Voluntary muscle and skeletal
• Proximal metabolic myopathy, principally affecting type II
• Neuromyopathy secondary to motor nerve damage
• Atrophy of smooth muscle of GI tract leading to motility disorders
• Osteopenia
• Gout
• Avascular necrosis (e.g. femoral head)
• Fractures (malunion)
Genitourinary and reproductive
• IgA nephropathy
• Renal tubular acidosis
• Renal tract infections
• Subfertility
• Impotence
• Spontaneous abortion
• Foetal alcohol syndrome

Contd...

Dermatological
• Skin stigmata of liver disease
• Skin infections bacterial, fungal, viral
• Local cutaneous vascular effects
• Psoriasis
• Discoid eczema
Haematological
• RBCs – Macrocytosis, anemia due to blood loss, folate deficiency and malabsorption
• WBCs – Neutropenia, lymphopenia
• Platelets – Thrombocytopenia
Social
• Family problems
• Marital discord
• Road accidents, driving offences
• Employment (e.g. absenteeism, poor performance, redundancy)
• Children's problem (e.g. stress, behavioural problems)
Psychological
• Anxiety (particularly social phobia), depression
• Personality change
• Misuse of other drugs
• Cognitive impairment
• Social phobia

Alcohol withdrawal syndrome is characterised by sympathetic nervous hyperactivity leading to sweating, tachycardia, hypertension and tremor. Clinical features (e.g. fatigue, weakness, hypertension, mental confusion, depression) may be partly related to, or a consequence of the excessive corticoid concentrations observed during withdrawal.

Clinical features. Marked variations in symptoms from one alcohol episode to the next, even in the same patient. However, individuals who have previously suffered from delirium tremens or seizures are likely to develop these again in subsequent withdrawal episodes.

Minor withdrawal: Features appear within a few hours after blood ethanol concentration declines sharply – weakness, faintness, sweating, irritability, catecholamine-induced hypertension, insomnia and tremors. Full recovery occurs within 24-72 hours.

Intermediate withdrawal: In addition to above features, patients may develop (a) Hallucinations (auditory or visual in nature), often with an unpleasant or threatening content. (b) Convulsions – Fits of the uncomplicated grand mal type. (c) Dysrhythmias are uncommon and probably occur secondary to hypokalaemia, hypomagnesemia and acid-base disturbances; they include paroxysmal atrial fibrillation, supraventricular tachycardia and ventricular tachycardia.

Major withdrawal: Delirium tremens – *Characteristic features:*

- Disorientation in time and space
- Hallucinations visual and sometimes auditory
- Extreme fear and apprehension leading to aggressive, destructive and suicidal behaviour
- Autonomic disturbances with tachycardia, fever, sweating, hypertension and pupillary dilatation

Management

Drug therapy – (a) *Benzodiazepines* – e.g. Chlordiazepoxide, lorazepam (b) *Carbamazepine* is useful in treating withdrawal features and seizures.

Other measures – Correction of electrolyte and acid-base disturbances, treatment of concomitant infection, adequate calories. B vitamin for Wernicke's encephalopathy.

Neuropsychiatric complications of chronic alcohol abuse

Wernicke's encephalopathy is an acute reaction to chronic thiamine deficiency.

Clinical Features

- *Ocular signs* – Combination of diplopia and strabismus (bilateral abducens and vertical and horizontal gaze palsies). Pupillary changes. Retinal haemorrhages and papilloedema can occur causing visual impairment.
- *Higher mental function disturbances* – Disorientation, confusion, recent memory lapses, poor attention and distractibility.
- *Others* – Polyneuropathy, ataxia are common. Marked malnutrition.

Neuropathology – Neuronal degeneration and hemorrhage in thalamus, hypothalamus, mammillary bodies and midbrain.

Korsakoff's psychosis – Wernicke's encephalopathy is often transformed into a relatively restricted Korsakoff amnesic state, characterized by gross disturbances of memory with confabulation and often impairment of insight. Main neuropathological lesion is in dorsomedial nuclei of thalamus and mammillary bodies. Changes also occur in periventricular and aqueductal grey matter, cerebellum and brainstem.

Marchiafava-Bignami disease – An uncommon disorder characterized by disorientation, fits, ataxia, dysarthrial hallucinations, spastic paresis and personality and intellectual deterioration. Dementia of subacute onset accompanied by prominent grasping and sucking reflexes.

Detection of Problem Drinkers

1. Questionnaires can be used; questions designed to reveal pattern of consumption as well as an estimate of the amount
2. CAGE questionnaire

- Have you ever felt you should **C**ut down on your drinking?
- Have people **A**nnoyed you by criticizing your drinking?
- Have you ever felt bad or **G**uilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?

Any single answer is probably significant; two positive answers almost certainly indicate alcohol dependence.

3. The AUDIT questionnaire performs better but is cumbersome.

Prevention of relapse in chronic alcoholism

1. **Alcoholic Anonymous** (AA) and the 12-Step Approach
   For the course of an individuals life to change, not only commitment to change is required, but at least one of the following conditions must be established:
   - A substitute for the dependency
   - Powerful new sources of self-esteem and hope
   - A new stable relationship

THE 12-STEP PROGRAMME

The language is couched in religious terms; seven of the steps mention God or a higher power and the programme has a spiritual quality:

1. Admitted we were powerless over alcohol that our lives have become manageable
2. Came to believe that a power greater than ourselves could restore us to sanity
3. Made a decision to turn our will and our lives over to the care of God as we understood him.

The remaining steps are reconcerned with faith, resignation, confession and spiritual reawakening. Referral to AA is simple – individuals may call the AA helpline or just attend a meeting. It is not necessary to be an 'alcoholic', the only requirement for membership is to stop drinking. Those who are unable to achieve stable recovery by merely attending meetings may be referred to a professional treatment programme, many of which are designed to help individuals affiliate with A.

PHARMACOTHERAPIES

Alcohol-sensitizing Agents

Disulfiram

Mechanism of action – Disulfiram inhibits aldehyde dehydrogenase, which is involved in the breakdown of ethyl alcohol. If alcohol is consumed, potentially toxic blood levels of acetaldehyde are produced, leading to facial flushing, tachycardia, hypotension, nausea and vomiting, difficulty in breathing, syncope, blurred vision and physical discomfort.

The intensity of the reaction varies with the amount of disulfiram and alcohol taken. Small amounts produce discomfort, but those who consume large amounts of alcohol experience severe, life-threatening symptoms which may last for many hours.

Contraindications – Pregnancy, severe cardiac disease.

Dose: 250–500 mg daily

Anticraving agents

Naltrexone – Mechanism of action: Alcohol consumption is reinforced by an interaction with the endogenous opioid system, and blocking opioid receptors with specific antagonists lessens the pleasurable effects of alcohol, thereby weakening the behavioural reinforcement and decreasing drinking. Side effects – headache and anxiety.

Dose: 50 mg/day.

Acamprosate – Mechanism of action – The drug is structurally similar to the amino acid taurine and acts as a GABA-receptor agonist.

Dose: 1332–1998 mg/day. Side effects: Diarrhoea.

Selection of pharmacotherapy – Disulfiram is usually reserved for individuals who have undergone several unsuccessful treatments and have suffered multiple relapses. The ideal patient for treatment with disulfiram is motivated for abstinence and willing to accept supervised administration of medication.

Naltrexone and acamprosate appear to be most effective in patients whose relapses are strongly related to alcohol craving and are effective in preventing relapses in alcoholics who return to drinking after achieving abstinence. The 'ideal' patient is one who has a strong craving for alcohol, is taking medication.

Detoxification for severely dependent patients requires hospital admission. *Indications* for in-patient detoxification are:

- Severe dependence
- History of fits

- History of delirium tremens
- Severe concurrent physical or mental illness, unsuccessful attempts at out-patient detoxification. Inadequate social support.

(For volatile substance abuse, see acute poisoning)

Opiate Abuse and Dependence

Opioid derivatives

a. *Natural alkaloids of opium:* Morphine, codeine, thebaine, noscapine, papaverine (b) *Synthetic derivatives:* Heroin, nalorphine, hydromorphine, methadone, pethidine, cyclazocine, levorphanol, diphenoxylate.

Heroin is more addicting than morphine in form of injection. In addition to parenteral use, heroin can also be smoked (or chased) often in the impure form (brown sugar or 'smack'). It can cause dependence after a brief period of use.

Clinical features include euphoria, apathy, psychomotor retardation, drowsiness, slurred speech, impairment of attention and memory.

Complications: (a) Due to contaminants: Parkinsonism, polyneuropathy, degenerative changes in globus pallidus, transverse myelitis, amblyopia. (b) Due to i.v. use: Skin infections, thrombophlebitis, endocarditis, septicaemia, HIV infection. (c) Social complication: Drug peddling and involvement in criminal activities.

Opiate withdrawal syndrome – Features include lacrimation, rhinorrhoea, pupillary dilatation, piloerection, sweating, diarrhoea, abdominal cramps, tachycardia, fever and insomnia.

ESTABLISHING DIAGNOSIS – Tests: (a) Naloxone challenge test to precipitate withdrawal symptoms. (b) Urinary opioid estimation by radioimmunoassay (RIA), free radical assay technique (FRAT), thin layer chromatography (TLC), enzyme-multiplied immunoassay technique (EMIT), etc.

Management

1. *Of opioid overdose* (*see* poisoning)
2. *Detoxification* – Techniques:

Use of substitute drugs, e.g. (a) Methadone, which is less addicting, with longer half-life and milder withdrawal symptoms. (b) Clonidine an α-2 agonist which inhibits release of norepinephrine at the synaptic receptors. Dose 0.3-1.2 mg/day initially, and then slowly reduced. Side-effects are sedation and postural hypotension. (c) Naltrexone and clonidine: Naltrexone, a narcotic antagonist causes withdrawal symptoms which can be countered by simultaneous use of clonidine for about 2 weeks, after which clonidine is stopped and naltrexone continued. Dose 100mg p.o. on alternate days.

Other drugs – LAAM (levo-alpha-acetyl methadol), propoxyphene, buprenorphine, phenoxylate and lofexidine.

3. *Maintenance therapy* – (a) Methadone 20–50 mg/day to shift the patient from 'hard' drugs, thus decreasing i.v. use. (b) Naltrexone 100 mg on Mondays and Wednesdays and 150 mg on Fridays. The drug combined with clonidine is very effective. (c) Other methods include individual psychotherapy, psychotropic drugs, behaviour therapy, family therapy and group therapy.

Cannabis

Preparations of cannabis are: Hasish/charas, gangja, bhang and hash oil (which is 25 times more potent than bhang). All the active ingredients of cannabis are labelled as marijuana (or marihuana).

Chronic abuse

1. *Transient disorders:* Acute anxiety, acute psychosis, hysterical fuge-like states, suicidal ideation, hypomania, schizophrenia-like state.
2. *Amotivation syndrome*: Lethargy, apathy, indolence, reduced drive.
3. *Cannabis psychosis* (Hemp insanity): Features similar to acute schizophrenic disorder with confusion and disorientation.
4. *Others*: Memory impairment, relapse in mood disorder or in schizophrenia, COPD, lung cancer, decreased immunity, diminished testosterone levels and spermatogenesis, anovulatory cycles, blocked gonadotrophic releasing hormone. Risk to the foetus during pregnancy.

Management is supportive and symptomatic. Antipsychotic drugs for psychiatric symptoms. Psychotherapy and family therapy.

CNS stimulants and Dependence

Cocaine can be taken orally, intranasally, by smoking or parenterally. It acts by inhibiting the uptake of dopamine along with that of norepinephrine and serotonin. A typical pattern of cocaine runs (binges) followed by cocaine 'crashes' from use interruption. Cocaine is at times used in combination with heroin ('speed ball') or with amphetamine.

Chronic abuse may lead to depression, memory loss, mania or paranoid psychosis. Myocardial fibrosis, cardiomyopathy, cerebral vasculitis, facial dystonic movements, preterm labour and foetal death have also been reported. Chronic intranasal use may cause perforation of nasal septum and CSF rhinorrhoea as a result of thinning of cribriform plate.

Withdrawal syndrome. Delirium, excessive fatigue, disturbed sleep, and increased dreams. A triphasic withdrawal syndrome ensues after an abrupt stoppage of chronic cocaine use (Table 22).

Complications: Acute anxiety reaction, uncontrolled compulsive behaviour, psychotic episodes (with persecutory delusions, and tactile and other illusions), and delirium. High doses of cocaine can induce fits, cardiac arrhythmias, respiratory depression, ischemic heart disease, lung damage, GI necrosis, foetal anoxia and nasal septum perforation.

MANAGEMENT. Before commencing therapy, coexisting psychiatric and/or physical disorder must be ruled out.

Table 22: Withdrawal syndrome phases

Phases	*Cl. Fs.*	*Duration*
I (crash phase) Substage 1 Substage 2 Substage 3	Agitation, depression, Anorexia, craving+++ Fatigue, depression, sleepiness, craving + Exhaustion, hyper-somnia with intermittent awakening, hyperphagia, craving±	9 hrs. to 5–7 days 4–7 days
II Substage 1 Substage 2	Normal sleep, improved mood, craving ± Anxiety, anergia, anhedonia, craving ++	4–7 days
III (Extinction phase)	No withdrawal symptoms, increased risk of relapse	After 7–10 days

13. CHRONIC FATIGUE SYNDROME (CFS)

It is a syndrome of severe fatigue associated with other somatic symptoms and considerable disability, but no clear-cut biomedical diagnosis.

RISK FACTORS

- CFS is more common in individuals who have had previous psychiatric illness
- Encephalitic illnesses, and perhaps other causes of CNS damage may predispose
- Lack of physical fitness (an important variable in previously fit individual who are forced into inactivity) may have a role in perpetuating CFS.

CLINICAL FEATURES

- Fatigue is central rather than peripheral in origin, neuromuscular function is usually normal.
- Cognitive dysfunction – Most memory functions are normal, though there are problems in selective attention. CFS may be associated with a disorder of effortful cognition, rather than any defects in recall.

COGNITIVE AND BEHAVIOURAL FACTORS IN CFS

Inactivity – Rest reduces activity tolerance, and has profound effects on cardiovascular and neuromuscular function. With time more symptoms and greater level of fatigue occur at lower levels of exertion.

Inconsistent activity. Typically, prolonged rest is followed by a burst of activity that is often 'too soon'. This often leads to complain of CFS sufferers that any activity must be 'paid for' later by pain and fatigue.

Illness beliefs and fears about symptoms can influence disability, mood and behaviour. In CFS unhelpful illness beliefs include fear that: (a) any activity that increases fatigue is damaging, (b) over-exertion causes permanent muscle damage, (c) CFS is irreversible or untreatable.

Symptom focussing. Increased concern leads to increased awareness, selective attention and 'body-watching' which can intensify and increase frequency of symptoms.

Emotional consequences. In some patients with CFS, depression may arise during the illness, with anxiety, frustration and boredom. Depression and anxiety are associated with fatigue and muscle pain, impaired memory and reduced activity.

Management – (a) Drugs: Various antiviral drugs and agents acting on the immune system have been tried. (b) Nutritional supplements. (c) Antidepressants for patients with depressive symptoms. (d) Rehabilitation remains the mainstay of treatment.

14. DELIBERATE SELF-HARM

AETIOLOGY

Sex and age – Self-harm occurs principally in young adults, more in females.

Social factors – (a) Incidence high in lower socioeconomic status and inhabitant of urban with socioeconomic deprivation and poor social integration. (b) A major argument or separation from the partner is the most common preceding event. (c) Unemployment and increased risk among individuals with epilepsy, particularly men. (d) Break-ups in relationship and problems in relationship with their parents (among teenagers).

Psychiatric disorder – Most common are depression, alcohol and drug abuse, anxiety and eating disorders. Also personality disorders, particularly of borderline and dissocial type. Some have psychotic disorders.

NATURE OF THE ACT

Self-poisoning is most common with psychotropic drugs, paracetamol, organophosphates, other pesticides and naturally occurring poisons.

Self-injury is usually by self-cutting, particularly of the wrist or forearm. Violent forms include gun-shot wounds, hanging, jumping in front of moving vehicles, severe lacerations.

Table 23 gives the risk of repetition of self-harm.

POTENTIAL PROBLEMS IN SUICIDAL PATIENTS

- Relationship with partner, spouse or other family members particularly with young children
- Employment or studies
- Finances
- Housing
- Legal
- Social isolation (relationship with friends)
- Alcohol or drugs
- Psychiatric disorder
- Personality disorder
- Physical illness
- Sexual adjustment
- Bereavement or impending loss
- Exam failure and failed love affairs in teenagers.

Deliberate self-harm following a recent separation or major argument is less often associated with eventual suicide. The ability of patients to cope can be assessed by asking: (a) who they turn to for help, (b) how they coped with past stressful events, (c) what they think they can do to overcome present difficulties.

After care. Psychiatric disorders require treatment by the usual approaches. Psychotropic medicine may be dangerous in overdose and should be used only when genuinely necessary. SSRIs may prevent repetition of self-harm in those with history of previous episodes. Neuroleptics may help some 'chronic repeaters' and long-term individual and group therapy may benefit some with borderline personality disorders who self-harm frequently. Provision of emergency excess to advise and help at times of future crisis may be helpful in some patients.

Table 23: Risk of repetition of self-harm

Factors associated with increased risk
Previous self-harm
Personality disorder
Alcohol abuse
Previous psychiatric treatment
Unemployment
Low social caste
Drug abuse
Criminal record
History of violence
Age 25–55 years
Single, divorced or separated
Risk of suicide
Factors suggesting serious suicidal intent
Act performed in isolation
Act timed such that intervention is unlikely
Precautions taken to avoid discovery
Preparations made in anticipation of death (e.g. making a will, organizing insurance)
Active preparations made for the act (e.g. saving tablets)
Telling others about intention before the act
Extensive premeditation (more than 3 hours)
Leaving a suicide note
Failure to alert potential helpers during or after the act
Admitting the act was intended to cause death

15. EATING DISORDERS

The term 'eating disorders' refers to a group of psychiatric disorders characterized by abnormal eating behaviour that is not caused by obvious organic disease. The two major eating disorders are anorexia nervosa and bulimia nervosa; a third is binge eating disorder.

ANOREXIA NERVOSA

The primary feature is weight loss.

- *In the restricting type,* patients achieve weight loss by eating restraint alone.
- *In the binge-eating/purging type,* patients may combine calorie restriction with other means of weight control such as self-induced vomiting and abuse of laxatives or diuretics.

Excessive exercise may also be used. Such patients often also binge eat.

Amenorrhoea probably occurs secondary to weight loss. In children, the disease may present often as a reduction in the expected rate of weight increase.

Epidemiology. Although eating disorders usually develop in adolescence and young adulthood, they can occur in the elderly and in children. Anorexia nervosa is more common in occupational groups such as dancers, models, and athletes, among whom thinness is highly valued.

Aetiology – is multifactorial, involving both biological and psychological factors. Twin studies suggest that genetic factors may predispose, and certain personality traits (e.g. perfectionism, emotional restraint, low self-esteem) also have a role. Sociocultural factors are important – anorexia nervosa is more common in industrialized nations than in the developing world.

Psychopathology. Patients are overconcerned about their body size and shape. Even when they know they are significantly underweight, they often feel fat and ugly; this is termed 'body image disturbance'. Fear of complete loss of control of eating if the rigid dietary restraint is relaxed is also more common in anorexia nervosa. Depression is common.

Diagnostic criteria

- Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss or failure to make expected weight gain during periods of growth, leading to body weight < 85% expected)
- Intense fear of gaining weight or becoming fat, even though underweight
- Disturbance in perception of body weight or shape, undue influence of body weight and shape on self-evaluation, denial of the seriousness of the current low body weight.
- Amenorrhoea in post-menarchal women.

Physical Complications

See Table 24.

Investigations

- Full blood count
- Urea and electrolytes
- Calcium, magnesium, phosphate
- LFTs and serum proteins
- ECG

Additional Investigations

- Vitamin B_{12} and folate
- RBC transketolase (thiamine)
- Dual-energy X-ray-absorptiometry

Table 24: Physical complications of anorexia nervosa

Gastrointestinal	**Metabolic and nutritional**
Dental erosion	Hypokalaemia
Parotid enlargement	Metabolic alkalosis
Oesophagitis	Hyponatremia
Mallory-Weiss tears	Hypochloraemia
Acute gastric dilatation on refeeding	Hypocalcemia
Abnormal LFTs	Hypomagnesemia
Pancreatitis	Hypophosphatemia
Delayed gastric emptying	Zinc deficiency
Constipation	Thiamine deficiency
Gastric and oesophageal perforation	Impaired renal concentration ability
	Refeeding oedema
Cardiovascular	**Haematological**
Bradycardia	Neutropenia
Hypotension	Anemia
Arrhythmia	Thrombocytopenia
ECG changes (prolonged QT, ST-T changes, decreased QRS amplitude)	**Musculoskeletal**
	Osteoporosis
Cardiac failure on refeeding	Proximal myopathy
	Endocrine
	Amenorrhoea
	Low testosterone
	High cortisol
	Skin
	Lanugo hair
	Dry skin
	Hypercarotenemia

Management

a. Out-patient

No form of individual psychotherapy has been shown to be superior to any other, and mostly an electric approach including elements of psycho-education is adopted. Medication has little role.

b. In-patient

Treatment is aimed at restoring normal weight while simultaneously addressing the underlying psychological problem. Refeeding programmes are designed to achieve a weight increase of 0.5–1 kg/week.

Indications for inpatient – (i) Very low weight or rapid weight loss. (ii) Serious physical complications. (iii) Severe psychiatric co-morbidity. (iv) Failed out-patient treatment. (v) Lack of out-patient facilities. (vi) Need for separation from family.

Treatment of physical complications – (a) Osteoporosis may lead to pathological fractures, replacement oestrogen therapy or calcium supplementation preparations can be prescribed. (b) Amenorrhoea usually resolves following restoration of normal weight.

BULIMIA NERVOSA

Aetiology. (a) It is likely that young women who develop bulimia nervosa are responding to similar cultural pressures, and the disorder commonly follows a period of attempted eating restraint. (b) About 30% suffered sexual abuse as children. (c) Genetic factors appear to be less important than in anorexia nervosa, but there is evidence of a role for the 5-HT neurotransmitter system, which is involved in the regulation of appetite.

Diagnostic criteria

- Recurrent episodes of binge eating
- Recurrent inappropriate compensatory behaviour to prevent weight gain
- Binge-eating and inappropriate compensatory behaviours occurring on average, at least twice weekly for 3 months
- Self-evaluation unduly influenced by body shape and weight
- The disturbance does not occur exclusively during episodes of anorexia nervosa

An episode of binge eating is characterized by:

- Eating in a short period of time (e.g. 2 hours) an amount of food larger than most individuals would eat during similar circumstances
- A sense of lack of control of eating (e.g. amount, type of food)

Physical complications

- Hypokalaemia
- Metabolic alkalosis
- Dental erosion
- Parotid enlargement
- Hyperamylasaemia
- Mallory-Weiss tears of oesophagus

Investigations

- Full blood count
- Urea and electrolytes
- Calcium, magnesium, phosphate
- ECG

Management – Cognitive behaviour therapy which requires 10–12 sessions of treatment. Admission to hospital may be required in patients with complicated types of the disorders (e.g. multi-impulsive). Fluoxetine 40–60 mg/day reduces the urge to binge in a good number of patients, and can be used as an adjunct to psychological treatment.

BINGE-EATING DISORDER

It is characterized by repeated binge-eating without the compensatory behaviours seen in bulimia nervosa. Consequently, most patients are overweight, and may represent a specific subgroup of the obese. These individuals have a higher level of general psychiatric morbidity. Some patients may benefit from psychological interventions. It is more common in obese and over-weight individuals.

16. CHILD PSYCHIATRY

ASSESSMENT OF PSYCHIATRIC DISORDERS IN CHILDREN

A psychiatric disorder can be defined as behavioural or emotional symptoms so prolonged or severe that they cause suffering to the child or to others, social restriction or impairment of development. Some symptoms (e.g. fire-setting in the home when others are asleep, delusions, deliberate self-harm) are so extreme that they are considered abnormal when they occur only once. Most symptoms, however are considered abnormal only if they persist, are seen in several situations and lead to impairment. Table 25 gives principal disorders in children.

Type of disorder. Different components of the child's problems are recorded separately using multiaxial classification:

- Axis 1 Clinical psychiatric syndrome
- Axis 2 Specific developmental disorders
- Axis 3 Intellectual level
- Axis 4 Medical conditions
- Axis 5 Abnormal psychosocial situations
- Axis 6 Severity of impairment

Assessment process

a. *Family interview* to determine how the parents respond to the child's communications (e.g. sympathetically, critically), whether parents have difficulties in their own relationship.

Table 25: Principal disorders in children
Emotional disorders
Anxiety
Depression
Somatization
Obsessive compulsive disorders
Behavioural disorders
Conduct disorders
Hyperkinetic disorder
Mixed disorders of conduct and emotion
Other disorders
Autism and related disorders
Schizophrenia
Enuresis and encopresis
Mental retardation
Learning disability
Academic backwardness
Epilepsy and its consequences
Brain injury in childhood
Disorders due to situations in the family

b. *Interview with the child.* Area to be assessed include general behaviour, dress and appearance, emotional responsiveness, habitual mannerisms, mood, preoccupations, speech, attention, activity level and cognition.

c. *Other sources of information* particularly the school.

MENTAL RETARDATION

Sub-average general intellectual functioning which originates in the developmental period and is associated with impairment of adaptive functioning.

Diagnosis of intellectual defect – Mental retardation should be suspected if any of the following are present in an individual:

1. **Clinical findings** – (a) History of mental deficiency in the family. (b) Home environment which hampers the development of mental potentialities due to inadequate intellectual, social and personality forming influences. (c) Evidence of anomalies of skull such as microcephaly, oxycephaly, hydrocephalus, asymmetry of skull and face, malformations of external ear, eye and nose; thickness of lips, protruding mandible, ill-formed teeth and deformities of palate. (d) Delay in physiological, psychological or social development, i.e. delay in the milestones. (e) Defect in articulation of speech and vocabulary. (f) Poor scholastic performance like repeated failures in examinations. (g) Short span of general information and practical knowledge. (h) Inefficiency in work and poor economic achievements.
2. **Intelligence Quotient (IQ) tests** – These tests are standardised and their reliability and validity indices fall within an accepted range. However, a patient's cooperation is necessary for proper assessment of these tests. Verbal and non-verbal (performance) items comprise the IQ tests from which the mental age of a patient can be determined. The IQ can then be calculated as follows:

$$\text{IQ} = \frac{\text{Mental age} \times 100}{\text{Chronological age}}$$

Average IQ = 90–110. IQ of 70 to 90 constitutes borderline mental retardation.

Grades of Retardation:

- Mild: IQ 50–70
- Moderate: IQ 35–49
- Severe: IQ 20–34
- Profound: IQ below 20

Aetiology: Several factors are incriminated, but in majority of cases, no cause can be found (idiopathic or subcultural). The factors could operate before, during or after birth, but before complete mental development is attained (Table 26).

Management

1. *Piracetam* – 40 mg/kg/day in divided doses, a nootropic drug is postulated to improve concentration and learning abilities of retarded children. No drugs, however, are available to increase the level of intelligence.
2. *Psychotropic drugs* – for associated behavioural abnormalities.
3. *Counselling of parents.*
4. *Education and training in schools* for the mentally handicapped.
5. *Appropriate rehabilitation* depending on each individual's level of intelligence and aptitude.
6. *Management of behavioural problems* by appropriate medication and behaviour therapy.

EMOTIONAL DISORDERS IN CHILDREN

1. **Anxiety disorders** are often exaggerations of normal development trends. Onset is usually during the developmentally appropriate age period. For example, it is normal for infants to show anxiety over separation

Table 26: Aetiology of mental retardation

1. ***Prenatal factors***
   a. Chromosomal abnormalities like Down's syndrome, Klinefelter's syndrome, Turner's syndrome.
   b. Inborn errors of metabolism – e.g. phenylketonuria, galactosaemia, mucopolysaccharidosis, Tay-Sachs disease, Gaucher's disease, etc.
   c. Cranial malformations – Hydrocephaly, microcephaly.
   d. Gross brain disease – Tuberous sclerosis, neurofibromatosis, cerebral palsy.
2. ***Perinatal factors***
   a. *Infections* – Rubella, cytomegalovirus, toxoplasmosis, syphilis.
   b. *Intoxications* – Certain drugs, lead, bilirubin (kernicterus).
   c. *Physical causes* – Injury, hypoxia, radiation.
   d. *Placental dysfunction* – Toxaemia, nutritional growth retardation.
   e. *Endocrine disorder* – Hypothyroidism
   f. *Birth trauma*
   g. *Prematurity*.
3. ***Postnatal factors***
   a. *Infections* – Meningitis, encephalitis.
   b. *Head injury* – Accidental, child abuse.
   c. *Intoxication* – Lead, carbon monoxide.
   d. Adverse family and sociocultural factors – Low socioeconomic status, poverty, poor housing, malnutrition, unstable family environment.

from those to whom they are attached – it is only when this anxiety causes impairment or persists into later childhood or adolescence, that separation anxiety disorder is diagnosed.

Aetiology – (a) Genetic factors: Children who are constitutionally 'slow to warm up' and inhibited are at greatest risk. (b) Anxious parents behaving overprotectively. (c) Some cases (particularly those caused by specific fears) are precipitated by stress.

Management – Reduction of stress, behavioural treatment of specific symptoms (e.g. graded exposure to the feared situation) and general treatment (e.g. relaxation). Anxiolytics are helpful in severe cases, but should not be prescribed for long periods.

2. **Depressive disorders** are uncommon in prepubertal children. Main clinical features are the same as in adult depression, but depressed children suffer more somatic complains and anxiety than adults. Infants who have been severely deprived or abused sometimes show a state of withdrawal retarded development (anaclitic depression).

   Children with depressive disorders tend to have parents who are depressed. About 50% of depressed children also have an anxiety disorder, and 20% have a conduct disorder.

   Management – comprises reducing adversity, behaviour therapy (to children > 10 years of age) and /or family support. SSRIs (e.g. fluoxetine, paroxetine) may be useful in severe cases. Supportive psychotherapy and family therapy is the key to effective therapy.

3. **Somatization.** Unexplained physical symptoms such as abdominal pain and headaches are associated with emotional disturbances, but most of the children are not otherwise psychologically disturbed. They tend to come from families in which there are health problems and high academic expectations. In many cases, the child is in a predicament from which there is no other means of 'escape'. Pre-existing physical problems in the child or in a relative may determine the type of symptomatology. Many children may develop these symptoms as an excuse to avoid exams and school after a long vacation.

Management – involves close liaison between psychiatrist and paediatrician, changing the family focus from physical to psychological issues, and an emphasis on the child leading as normal a life as possible (e.g. returning to school).

4. **Obsessive compulsive disorder.** Obsessions are a normal part of child development. In middle childhood, obsessional acts such as avoidance of stepping on cracks in the pavement are common, in late childhood, obsessive collection of objects (e.g. stamps). The most common presenting obsessions are fear of dirt, fear that something terrible will happen, and fear of disorder. The most common compulsions are washing rituals, repeating rituals and checking.

   Obsessive-compulsive symptoms are often found in conjunction with other emotional disorders. Onset tends to be earlier in boys than in girls. Childhood onset OCD is associated with basal ganglia disease, a family history of disorder or tics, and family stress.

   Management – Behavioural interventions such as response prevention, and SSRIs (e.g. fluoxetine) or clomipramine.

5. **School attendance problems.** Some form of emotional disorders are often present, but the most common reason for failure to go to school is truancy, in which absence of school is concealed from parents. School refusal can be a symptom of any form of emotional disorder, particularly separation anxiety. Complaints of illness are often used, and abdominal pains may occur on school days (periodic syndrome).

Management depends on the cause. Close liaison with the school and educational welfare service are important.

6. **Enuresis and encopresis**

Table 27: Components of hyperactivity

Attention deficit
• Fails to give attention
• Does not listen
• Easily distracted
• Forgetful
• Does not copy notes completely
• Loses things in the school
Hyperactivity
• Excessive movements
• Fidgety
• Has difficulty playing quietly
• Talks excessively
Impulsivity
• Often acts without thinking
• Reckless
• Difficulty taking turns
• Interrupts others

Childhood enuresis (*see* diseases of children)

Encopresis is involuntary passage of faeces into clothing after the age at which bowel control is usual and in absence of a known organic cause.

Aetiology: (a) Poor toilet training. (b) Environ-mental stress, e.g. following birth of younger sibling, conflict between parents illness of parent.

Encopresis like enuresis could be present from birth (primary) or could appear after a sustained period of continence (secondary).

Management: (a) Counselling regarding faulty toilet training. (b) Behaviour therapy to encourage child to remain continent. Medication may be needed when aggression is very high. Supportive psychotherapy and family therapy essential.

BEHAVIOURAL DISORDERS IN CHILDREN

1. **Conduct disorders** – are characterized by repetitive antisocial behaviour that lasts for at least 6 months. In young children, the clinical picture is dominated by markedly oppositional behaviour such as defiance, hostility and disruptiveness. In older children behaviours such as stealing, truancy, lying and running away are seen. In the most severe cases, fire-setting or cruelty to animals may occur.

Aetiology – (a) Twice more common in boys. (b) Strong link with family dysfunction, particularly discordant intra-family relationships. (c) Genetic factors role is unclear, though temperamentally 'difficult' babies seen to be at a greater risk.

Management – Parenteral skills training encouraging the parent to monitor child's behaviour, to become more involved with the child, to discipline the child more effectively, and to encourage pro-social behaviour. Severely disturbed children may benefit from placement in a special school or other residential setting.

Table 28: Differential diagnosis of hyperkinetic disorders

1. **Normal developmental variation**
2. **Co-morbid conditions**
– Conduct disorder
– Pervasive developmental disorders (e.g. autism)
– Specific developmental disorder (e.g. language disorder)
– Mental retardation
3. **Disorders affecting activity level or attention**
– Anxiety disorders
– Mood disorders (e.g. mania, depression)
– Substance abuse
– Attachment disorders

2. **Hyperkinetic disorders** are characterized by early onset of overactive behaviour, impulsiveness and marked inattention (Table 27). The disorder is four times more common in boys.

Aetiology. Brain dysfunction resulting from genetic processes or early brain damage is important. Hyperkinesis may occasionally result from early social deprivation. It is also associated with family discord.

Several other abnormalities are associated with the disorder, including conduct disturbances and learning difficulties. See Table 28 for the differential diagnosis of hyperkinetic disorders.

Management

1. *Biological factors* (a) Environmental manipulations such as starting fulltime school. (b) Behaviour modification programmes that encourages the child to concentrate for increasingly lengthy periods. Modifying the child's diet may help.
2. *Stimulant medication* (e.g. methylphenidate) in a dose of 5–10 mg/day for 1 week initially, increasing to 20–40 mg/day depending on response. Dexamphetamine can be used as an alternative in children under 6 years of age. Side effects – Long-term effects on growth are uncertain, dysphoria, tics and poor sleep. Newer drugs like Atomoxetine 10–40 mg/day may be used in some cases.

3. *Mixed disorders of conduct and emotion* are characterized by a mixture of emotional and behavioural problems. About 20% of children also have conduct disorder ('depressive conduct disorder'). Treatment is symptomatic.

LEARNING DISABILITY

Learning disability is defined as a significant impairment of intelligence and social functioning acquired before adulthood.

Aetiology

- It is more common in males. Some affected family members have psychiatric disorder without learning disability.
- Metabolic causes (e.g. phenylketonuria)
- Infections (e.g. cytomegalovirus, rubella, measles, AIDS) are important causes in perinatal period
- Injury in childhood may cause permanent brain injury
- No identifiable cause
- Co-morbid conditions including increased prevalence of epilepsy, psychiatric disorders, hearing and visual impairment, autism.
- Two main characteristics are manifested in the developmental period
- No known medical cause is required

Co-morbidity – Epilepsy in about one third with severe learning disabilities, often presenting at puberty. Depression is common in adults with learning difficulties, but may remain undiagnosed because of atypical presentation (e.g. irritability, aggressive outbursts, loss of interest, with or without disturbance of sleep or appetite).

Management – (a) Regular health checks to exclude sensory problems, thyroid disease, depression and other co-morbidity conditions. (b) Multidisciplinary assessment advisable.

AUTISM

Diagnostic Criteria

- Qualitative impairment in social interactions
- Qualitative impairment in verbal and non-verbal communication
- Restrictive, repetitive and stereotyped patterns of behaviour, interests and activities

Social impairment comprises limited eye contact and little use of body language and facial expression. Autistic children often lack any interest in social activities. If they do try to make friends with children of their own age, they are usually rebuffed because of social ineptitude.

Communication impairment – Many autistic children with low IQ do not develop useful speech. Language development is usually delayed and they do not use non-verbal gestures in compensation (unlike deaf children, with whom they may be confused initially).

Behaviour – The behaviour of autistic children is stereotyped, and lacks imagination. Many such children flap their hands or spin when excited or upset. Others have bizarre preoccupation with the feel, taste or smell of certain objects such as sand, water or metal.

Intelligence – 75% of autistic individuals have an IQ of < 70, and of these, two-thirds < 50. Typically, non-verbal abilities are considerably better than verbal skills.

Pervasive developmental disorders. In addition to the core syndrome, the ICD-10 classification includes conditions that are autistic-like (termed pervasive developmental disorders, PDDs) including Asperger's syndrome. Typically PDDs are less severe than autism, and social communication deficit is usually the main clinical feature. Asperger's syndrome may be indistinguishable from high-functioning autism, but lacks a significant delay in cognitive and language development. Motor clumsiness and circumscribed interests dominate the clinical picture.

Aetiology: Autism is a strongly heritable disorder and the genetic predisposition is polygenic but none of the genes have been identified. Mild impairment of social communication skills is more commonly found in first-degree relatives, affecting upto 10%, particularly males. Viral hypothesis as well as biological factors and vaccine-related side effects have been proposed as causative factors.

Investigations. In addition to IQ and formal language skills, EEG, screening for fragile X and chromosomal anomalies and a brain scan may be necessary.

Associated disorders. Risk of autistic-like symptoms is increased in tuberous sclerosis, and may be increased in some genetic anomalies (e.g. fragile X syndrome, certain structural anomalies of chromosome 15q, Turner's syndrome). Some children develop seizures in infancy (usually infantile spasm).

Differential Diagnosis of autism includes hearing problems, receptive-expressive language disorders and global intellectual delay. However children with these conditions do not have difficulties in making social relationships, and do not engage in repetitive behaviours or rigid routines to the same extent as those with autism.

Management. (a) Developing communication: Education provision should aim to maximize social, communicative and intellectual functioning. In some cases, behavioural interventions to reduce repetitive, stereotyped, self-injurious and challenging behaviours. (b) Medication: Neuroleptics (e.g. haloperidol) for stereotyped behaviours and hyperactivity. Risperidone to relieve anxiety, aggression and repetitive behaviour. SSRI (fluoxetine) could ameliorate autistic symptomatology.

17. DRUG-INDUCED PSYCHIATRIC DISORDERS

CLASSIFICATION

1. ***Behavioural toxicity***
   a. *Drowsiness* – Benzodiazepines, neuroleptics, antihistaminics, antidepressants, antihypertensives.
   b. *Behavioural changes* – consisting of irritability, aggressive outbursts and a generalised hostile attitude: Benzodiazepines, barbiturates, levodopa, neuroleptic drugs, alcohol, drug-withdrawal states. Some tricyclic antidepressants, selective serotonin uptake inhibitors.
2. ***Delirium (Acute organic psychosis)***
   a. Cardiovascular drugs – Digitalis, diuretics, propranolol, pindolol, oxprenolol. (b) Anticholinergics – atropine, homatropine, scopolamine, antiparkinsonian drugs, tricyclic antidepressants. (c) Tranquillizers and hypnotics – barbiturates, benzodiazepines, antidepressants, phenothiazines, bromides. (d) Antituberculous drugs – Isoniazid, rifampicin, cycloserine. (e) Anticonvulsants – Phenytoin, sodium valproate. (f) Miscellaneous drugs – Corticosteroids, insulin, disulfiram, cimetidine, chloroquine, aminophylline, oral hypoglycaemic agents. (g) Drug withdrawal – Barbiturates, benzodiazepines, chlormethiazole, dextropropoxyphene, alcohol, opiates, phencyclidine.
3. ***Affective states*** –

Depression – (a) Antihypertensive agents –reserpine, alpha methyl dopa, clonidine, propranolol, pindolol. (b) Corticosteroids. (c) Psychoactive drugs – phenothiazines, neuroleptics, benzodiazepines. (d) Antiparkinsonian agents – Levodopa. (e) Analgesics – Indomethacin, pentazocine. (f) Hormones – Oestrogens, oral contraceptives. (g) After withdrawal of CNS stimulants – amphetamines, cocaine. (h) Miscellaneous drugs – Ethanol, antineoplastic agents, disulfiram, tetrabenazine, phenytoin, phenobarbitone, theophylline, digoxin, danazol, cimetidine, chloroquine, cycloserine.

Elation – (a) Antidepressants. (b) Corticosteroids. (c) Anti-parkinsonian agents – benzhexol, procyclidine, levodopa, bromocriptine. (d) CNS stimulants – amphetamines, cocaine, methylphenidate. (e) Miscellaneous – Isoniazid, aminophylline, cyclizine, yohimbine, salbutamol, clonidine withdrawal.

4. ***Psychotic states*** –
   a. Hallucinogens – LSD, cannabis, phencyclidine. (b) CNS stimulants – Cocaine, amphetamines. (c) Appetite suppressants – Phenmetrazine. (d) Sympathomimetics – Ephedrine, pseudoephedrine, phenylephrine. (e) Alpha-adrenergic agonists – phenylpropanolamine. (f) Beta-adrenergic agonists – Salbutamol. (g) Beta-adrenergic antagonists – Propranolol, oxprenolol. (h) Dopaminergic drugs – Levodopa, dopamine, bromocriptine. (i) Narcotic analgesics – Pentazocine. (j) Corticosteroids. (k) Non- steroidal anti-inflammatory agents – Indomethacin. (l) Anti-depressant drugs. (m) Anticholinergic drugs. (n) Miscellaneous – Disulfiram, anti-tuberculosis drugs, cimetidine, antihistaminics, digoxin, methyldopa, phenytoin.
5. ***Pseudodementia*** – Benzodiazepines and barbiturates, major tranquillizers, anti-hypertensives, diuretics, antiparkinsonian drugs and digoxin in the elderly, and overdose of antiepileptic drugs in some epileptics. Chronic hypoglycemia due to oral hypoglycaemic drugs or insulin.
6. ***Neuropsychiatric states*** – Combinations of psychiatric and neurological symptoms and signs. Phenytoin can induce a paranoid-hallucinatory psychosis or delirium with cerebellar signs and symptoms. Neuroleptics can produce extra-pyramidal reactions like akathisia, pseudo-parkinsonism, acute dystonias and tardive dyskinesia.

18. TREATMENT METHODS IN PSYCHIATRY

I. **Psychotherapies**

Psychotherapy is an effective primary treatment for many psychiatric disorders. A range of different psychotherapies is now available that can be matched to the illness and personality of the individual patient (Table 29).

Assessment – Despite the overlap between different psychotherapies, assignment of patients to an appropriate therapy is a central psychotherapeutic task.

Table 29: Psychiatric disorders and their psychiatric treatment
Schizophrenia
• Cognitive behaviour therapy for delusions and hallucinations
• Family intervention to reduce expressed emotion
Depressive disorders
• Cognitive behaviour therapy, interpersonal therapy or brief dynamic therapy for mild-to-moderate depression
• Supportive psychotherapy or psychoanalytical psychotherapy for chronic dysthymia
Anxiety disorders
• Behaviour therapy
Obsessive compulsive disorders
• Behaviour therapy
Eating disorders
• Family therapy
• Cognitive behaviour therapy
• Psychoanalytical psychotherapy
Borderline personality disorder
• Psychoanalytic psychotherapy
• Dialetical behaviour therapy
• Supportive psychotherapy
Post-traumatic stress disorder
• Cognitive behaviour therapy
Abnormal grief reactions
• Guided mourning
Learning difficulties
• Creative therapies
Somatoform disorders
• Cognitive behaviour therapy

The dynamic loop – The mind can be considered to maintain a dynamic equilibrium, both internally and in relation to the environment. There is a hierarchy of interlocking psychological structures and mechanism comprising basic assumptions about the world, expectations about relationships ('object relations') and manifest behaviour connected via feedback loops that exist between individuals and their intimates. Psychotherapies aim to intervene at a number of points in this chain, hoping that changing one part will have an effect through the whole system.

Counselling – Compared with formal psychotherapy, counselling tends to be time-limited and less intense, and is undertaken at the level of primary rather than secondary services.

Main Groups of Psychotherapies

1. **Psychoanalytic psychotherapy** – is particularly appropriate to patients with borderline personality disorder or repeated relationship difficulties, or some psychosexual disorders, and sometimes in those with chronic mild depression.

TECHNIQUES – Psychoanalysis attempts to recreate and so reveal the unconscious assumptions, attitudes and desires that motivate patients, and which have led to their difficulties. The main vehicle for such revelation is the transference relationship with the therapist. The process is slow, and working through insights takes time, particularly in the highly disturbed patients to whom the therapy is usually offered.

2. **Brief dynamic therapy** (focal therapy). Here the therapist is more active than in psychoanalytic psychotherapy, often initiating and guiding sessions rather than waiting passively for the patient to reveal material.

Indications – Patients with circumscribed disorders (e.g. mild-to-moderate depression, anxiety states), who are well motivated, and are not actively suicidal or abusing drugs or alcohol. Although improvements in brief dynamic therapy tend to be maintained for upto 1 year, some patients require continuous treatment because relapse rate is high.

3. **Behaviour therapy**

Indications – Phobic disorders such as agoraphobia, specific phobias, social phobia and panic disorder. Standard treatment (often with clomipramine) for obsessive compulsive disorder, learning difficulties, severely disturbed patients.

Technique – ABC principle of:

- Antecedents
- Behaviour
- Consequences

Treatment comprises:

- Teaching the patient anxiety reduction techniques (e.g. deep relaxation)
- Graduated exposure to the feared stimulus, usually using positive reinforcement in the form of encouragement from the therapist, who maintains an uplifting attitude.
- Occasionally, negative reinforcement (e.g. snapping a rubber band on the wrist whenever an unwanted thought intrudes into the mind).

- Active collaboration between therapist and patient, in which patients are encouraged to become 'scientific observers' of their difficulties by recording their behaviour, and are set 'homework' aimed at modifying it. Contingency is a useful technique in behavioural family work, e.g. patients might be offered a reward in return for getting out of bed at an agreed time.

4. **Cognitive behavioural therapy (CBT)** – Techniques used in cognitive behaviour therapy are problem-oriented, aimed at changing errors or biases in cognition by appraisal of situations and stresses, and may modify assumptions about self, the world and the future. See Table 30 for the indications for cognitive behaviour therapy.

Cognitive therapies are two groups of skills: (a) *General therapeutic skills* are the basis. They are probably essential for engaging patients in treatment and maintaining the relationship and include setting a common agenda for therapy, (ii) eliciting feedback frequently, (iii) developing understanding and empathy, (iv) demonstrating interpersonal effectiveness, (v) maintaining collaboration, (vi) pacing and efficient use of time. (b) *Conceptualization, strategy and techniques* are more specific to cognitive behaviour therapy, e.g. patients can benefit from reading relative supporting literature, or from undertaking tasks to explore their problems further (e.g. completing diary sheets about panic attacks).

5. **Systemic (family/marital) therapies** are concerned with:

- How power is distributed between parents and children, and between men and women (e.g. do all have an equal voice, or are only certain family members heard?)
- How communication occurs and between whom (e.g. are communication 'routed' through one family member or is there free flow?)
  - How close or detached are individual family members?
  - What 'skeletons should be left in the cupboard'.
  - Family work is increasingly used in schizophrenia and can help reduce relapse rates in high 'expressed emotion' families.

6. **Creative ('humanistic') therapies** – constitute a heterogenous group of therapies including psychodrama, art, music and movement therapies and Gestalt therapy. Their common themes include:
   - Creative expression as a means of restoring self-esteem
   - Doing rather than talking (e.g. in Gestalt therapy, who is expressing anger towards a patient might be encouraged to 'put' that parent in an empty chair and speak to him or her as if present)
   - An emphasis on here and now rather than past experiences.
   - Creative therapies are particularly helpful in patients for whom verbal expression is problematic because of alexithymia (inability to put feelings into words).

7. **Integrative therapies** – Because patients often have a range of different problems (e.g. agoraphobia and marital difficulties), it can be helpful to combine or integrate therapeutic strategies.

Table 30: Indications for cognitive behaviour therapy

• Depression (particularly long-standing)
• Panic disorder
• Physical symptoms of 'unknown' origin including chronic fatigue syndrome
• Bulimia nervosa
• Obsessive-compulsive disorder
• Personality disorder
• Schizophrenia

'Conversational model' is a brief expressive therapy that has been used effectively to treat chronic functional bowel disease, depression and chronic non-psychotic psychiatric outpatients.

Interpersonal therapy is a ten-session course of therapy combining cognitive, marital and dynamic therapeutic approaches. It is effective in treating neurotic disorders, mild depression and bulimia nervosa. It focuses on the patient's current life situation and relates difficulty to unresolved grief, 'transitions' (e.g. leaving home, retirement), relationship conflicts with partners, and social skill deficits. Each is tackled using an appropriate technique.

Cognitive analytic therapy is a 16-session therapy combining a dynamic focus on the relationship with the therapist, a 'formulation' based on the idea that neurotic patterns are self-perpetuating, and a cognitive emphasis including keeping a mood diary and self-rating target problems.

Dialetical behaviour therapy combines cognitive behavioural approaches with a Zen Buddhist technique that helps patients maintain 'attentional focus' and thus be less tempted to self-harm.

8. **Group therapies** – 'Group analysis' combines psychoanalytic and sociological thinking. Therapeutic factors in groups include:
   - Mutual support and challenge of fellow sufferers
   - Seeing one's own problems from the outside, through the eyes of, or enacted by another
   - Reduced isolation and stigmatization (I am not the only one)
   - A sense of belonging
   - The power of the group matrix to hold and tolerate one's disturbance
   - Identification of both strengths and weaknesses.

   Groups may be long-term or short-term, closed or 'slow-open', analytic, behavioural or humanistic.

9. **Supportive psychotherapy** is integral to routine psychiatric practice, and covers at least three different types of therapies:
   - Brief counselling and support given to patients who are in crisis, often associated with bereavement or trauma
   - Non-intensive psychoanalytical therapies (psychoanalytical psychotherapy)
   - Formal but non-intensive therapy, often for highly disturbed patients who can be 'held' in supportive psychotherapy but are unsuitable for other forms of therapy.

10. **Hypnosis** – is a psychotherapeutic technique in which the person either by himself or with professional help, achieves a stage of concentration (hypnotic trance), characterized by high degree of focal attention with diminished awareness about the surroundings resulting in highly receptive state to suggestions.

Changes during hypnotic trance

- The individual under hypnosis becomes highly suggestible to the commands of the hypnotist not understanding their nature.
- Dissociation of a part of the body or emotions from the remainder may occur
- Partial or complete amnesia for events during hypnotic trance
- Ability to produce or remove symptoms, perceptions and/or movements
- Suggestion given soon after the trance are followed by the hypnotized person.

Assessment of hypnotic capacity, suggestibility and cooperation for the procedure – Eye roll sign: Those who have an impressive capacity to roll their eyes upwards while closing them are highly hypnotizable. Also those who are suggestible and willing to cooperate for the procedure can be easily hypnotized.

Indications

- Hysteria
- Psychosomatic disorders
- Phobic disorders
- Somatoform disorders (e.g. chronic pain)
- Habit disorders (e.g. smoking)

Contraindications – Suspicious and paranoid patients, since it can flare up the psychosis.

II. **Psychopharmacology**: (*see* antipsychotic drugs)

III. **Electroconvulsive therapy (ECT)** includes induction of seizures by passing an electric current through electrodes passed across the scalp.

Mechanism of action. It is postulated to be due to changes in neuro-transmitter metabolism and in the permeability of the blood-brain barrier that result from the passage of the electric current. ECT possibly affects the catecholamine pathways between diencephalon (site from where seizure generalization occurs) and limbic system (responsible for mood disorder), also involving the hypothalamus. ECT also causes downregulation of B_1 receptors in cortex and hippocampus.

Indications

- Major depression
- Not responding to antidepressant drugs
  - With psychotic symptoms
  - With failure to eat and drink
  - With depressive stupor
  - With high risk of suicide
- Schizoaffective depression
- Mania not responding to drug treatment
- Catatonia
- Postpartum affective psychosis

Suggestive indications

- Organic mental disorder, e.g. organic mood syndrome, organic hallucinosis, organic delusional disorder and delirium
- Medical disorders (e.g. organic catatonia, hypopituitarism, intractable seizure disorder, neuroleptic malignant syndrome, Parkinsonism)

Contraindications

Absolute: Raised intracranial pressure

Relative:

- Recent myocardial infarction
- Severe hypertension
- Cerebrovascular accident
- Severe lung disease
- Pheochromocytoma
- Detachment of retina

Pre-treatment evaluation

1. Informed consent from patient, guardian or relatives
2. Physical fitness
3. Laboratory investigations: Hb, total blood count, ESR, urinanalysis, ECG, chest radiograph

Patient preparation

1. Overnight starvation
2. Bladder (and bowel) should be emptied
3. Removal of dentures and loose teeth if any
4. Removal of tight clothing and metallic objects from the body

Technique

1. Inj. atropine (0.6 mg) i.m. 1/2 hr. before ECT
2. Anaesthesia: Thiopental sodium 5 mg/kg body wt. followed by:
3. Muscle relaxant: Succinylcholine 1 mg/kg body wt.
4. Mouth gag between the teeth to prevent tongue and lip bite

ECT – Two electrodes are placed bifrontotemporally on the scalp, 100–140 volts current is passed through the electrodes for 0.6–0.8 seconds from the ECT machine.

Seizure activity lasts for about 25–30 seconds.

Patient recovers consciousness with 15–30 minutes.

Number and spacing of treatment is determined by the clinical response. On an average 6–10 ECTs are required. Treatment is given 2 or 3 times a week.

Adverse Effects

- *Due to general anaesthesia*, succinylcholine (in patients with deficiency of pseudo-cholinesterase) and drug interactions. Memory disturbances (both antegrade and retrograde) are usually mild and recovery occurs within 1-6 months.

Post-treatment

- Postictal confusion
- Transient cardiac arrhythmias
- Prolonged apnoeic state
- Complications due to seizures (tongue bite, backache, fracture)

Drug interactions – It may be more difficult to induce effective seizures in patients taking drugs that elevate the seizure threshold (e.g. benzodiazepines, anticonvulsants). Antidepressant drugs such as tricyclics and SSRIs can lower the seizure threshold and prolong the duration of convulsions. If lithium is given during the course of ECT, the blood levels should be maintained at the lower end of the therapeutic range.

Duration of treatment and maintenance therapy – The number of ECT treatments is usually six to ten. ECT is effective in resolving acute depression or mania, but appropriate prophylactic drug treatment must be given once the course of treatment is completed. Relapse rates are high in patients who have received what would be considered adequate antidepressant drug treatment before ECT and who are maintained on same drug regimen. Hence, another class of antidepressant or lithium prophylaxis should be considered if it has not been tried previously. Some patients with frequent relapses that respond only to ECT can be considered for maintenance ECT in which treatment is given every 2 weeks or monthly.

IV **Magnetic field to externally stimulate brain cells**

Indications

1. Major depressive disorder
2. Treatment resistant depression
3. Auditory hallucinations
4. Schizophrenia
5. Bipolar disorder
6. Obsessive compulsive disorder
7. Eating disorder such as anorexia and bulimia

Advantages

a. Few or side effects
b. Quick onset of therapeutic effect (2 to 4 weeks)
c. Painless procedure
d. Non-invasive
e. No anaesthesia required
f. Outpatient therapy

V **Psychosurgery** is a surgical intervention to sever fibres connecting one part of the brain to another, or to remove, destroy or stimulate brain tissue, with the intent of modifying behaviour, thought or mood disturbances for which there is no underlying organic pathology (i.e. the disturbance is functional).

Aim of psychosurgery is to produce surgical lesions in selected sections of the limbic system or its connecting fibres. One major section of the limbic

system, believed to play an important role in emotional reactions is *Papez circuit* within which lies the limbic system, connecting cingulate bundle, hippocampus, anterior thalamus, mammillary bodies, fornix and septum.

Indications

1. Conditions which have failed to respond to all available treatments:
   - Chronic, severe, incapacitating depression
   - Chronic, severe, incapacitating OCD
   - Chronic, severe, incapacitating anxiety disorder
2. Schizophrenia with severe depressive component.
3. Severe, pathological and uncontrolled aggressive behaviour associated with a psychological or neurological affection (e.g. temporal lobe epilepsy).

Techniques used are stereotactic methods

1. *Stereotactic subcaudate tractotomy* for severe depression or anxiety, OCD and schizoaffective disorder.
2. *Stereotactic limbic leucotomy*. In addition to a lesion in cingulate bundle, a small subcaudate lesion is also made. It is used for treatment of OCD and schizophrenia.
3. *Amygdalotomy* is employed for severe, pathological, uncontrolled and intractable aggression associated with neuropsychiatric disorders.

Assessing the confused patient

Confusion may be a symptom of:

- Physical illness with metabolic disturbances that disturb brain function
- Systemic or brain infections
- Psychiatric disease
- Neuropsychological testing

A core feature of acute confusional states is disturbed selective attention, in which the patient is distracted by irrelevant environmental stimuli. Poor attention interferes with short-term memory and may be demonstrated by poor performance on digit span tests.

Disorientation in time and space is more common, disorientation for person is less common. Profound fluctuation in performance may occur across the whole rate of cognitive testing.

Biofeedback – is the use of an electronic instrument which provides immediate feedback to the patient regarding his physiological activities normally not available to the conscious mind, e.g. ECG, EEG, pulse rate, BP, EMG, galvanic skin response. The feedback helps the patient to control these responses. Relaxation is easily achieved by this method.

Other uses of biofeedback – Treatment of enuresis, migraine or tension headaches, incontinence, essential hypertension, cardiac arrhythmias, uncontrolled generalized tonic clonic seizures and for neuromuscular rehabilitation.

Interpersonal social rhythm therapy (IPSRT) – Bipolar I disorder is associated with persistent deficits in functioning over time, and for many patients psychosocial functioning remains markedly impaired. IPSRT is a novel, present-focused inter-personal psychotherapy in which the core deficit in bipolar disorder is considered to be instability, and disturbed biological rhythms are thought to arise from disruptions of social routine. IPSRT appears to be beneficial in reducing the time to recovery in bipolar depressive episodes, but this form of psychotherapy has not been useful in preventing relapse.

Omega-3 fatty acids – Eicosapentaenoic acid (EPA) and docosahexaenoic acid supplements, used as maintenance therapy, improve symptoms in patients with bipolar disorder.

Vagus nerve stimulation (VNS) involves stimulation of the left vagus nerve at the cervical level. The vagus nerve is anatomically linked to structures in the brain that are related to mood disorders. Available data suggest a sustained antidepressant effect in moderately medically resistant major depression.

VI **Psychoanalysis** denotes the following:

1. A psychological theory of mind and personality development based mainly on the concept of intrapsychic 'conflict'.
2. A procedure for the investigation of unconscious physical processes, otherwise inaccessible.
3. A therapeutic method of treating psychiatric disorders by psychological means.

ADDENDUM

Acute Confusional State

A core feature of acute confusional states is disturbed selective attention, in which the patient is distracted by irrelevant environmental stimuli. Poor attention interferes with short-term memory and may be demonstrated by poor performance on digit span tests.

Disorientation in time and space is more common, disorientation for person is less common. Profound fluctuation in performance may occur across the whole rate of cognitive testing.

Psychiatric Disorders in the Elderly

Organic

- Acute confusional states (delirium)
- Chronic confusional states (dementia)

Functional

Affective disorders

- Depression
- Mania
- Anxiety (generalized, phobic)

Schizophrenia-like

Adjustment disorders

- Bereavement

Abreaction is a procedure which brings to the awareness, for the first time, unconscious conflicts and associated emotions.

Abreaction methods:

With medication – 5% amytal or pentothal 500 mg in 10 mL normal saline infused at the rate of 1 mL/min.

Indications for amytal interview: (a) Abreaction(e.g. in hysteria). (b) Mute patient. (c) Diagnostic test in catatonic syndrome. (d) Differentiating test in stupor (for differential diagnosis of depression, schizophrenia, hysteria and organic brain disorders).

Contraindications: (a) Airway disease. (b) Severe renal or hepatic dysfunction. (c) Hypotension. (d) Porphyria. (e) Barbiturate dependence. (f) Psychosis (not catatonia or stupor).

Other uses of biofeedback – Treatment of enuresis, migraine or tension headaches, incontinence, essential hypertension, cardiac arrhythmias, uncontrolled generalized tonic clonic seizures and for neuromuscular rehabilitation.

Interpersonal social rhythm therapy (IPSRT) – Bipolar I disorder is associated with persistent deficits in functioning over time, and for many patients psychosocial functioning remains markedly impaired. IPSRT is a novel, present-focused inter-personal psychotherapy in which the core deficit in bipolar disorder is considered to be instability, and disturbed biological rhythms are thought to arise from disruptions of social routine. IPSRT appears to be beneficial in reducing the time to recovery in bipolar depressive episodes, but this form of psychotherapy has not been useful in preventing relapse.

Table 31: Clinical specialities and Munchausen's syndrome

Orthopaedics	Low back pain
Obstetrics and gynaecology	Pelvic pain, premenstrual syndrome, vaginal discharge
Otorhinolaryngology	Tinnitus
Neurology	Headache, dizziness
Cardiology	Atypical chest pain, palpitations
Pulmonary	Hyperventilation, dyspnoea
Dentistry	Temporomandibular joint syndrome
Rheumatology	Fibromyalgia (aches and pains)
Internal medicine	Chronic fatigue
Gastroenterology	Irritable bowel, functional dyspepsia

Psychoeducation – In treatment of bipolar I and bipolar II disorder, group psychoeducation reduces the number of patients who relapse and the number of recurrences per patient, and increases the time to depression and to manic, hypomanic and mixed occurrences.

Epidemiology of autistic spectrum disorder (ADS) – Recently autism has been conceptualized as a spectrum of related diagnostic categories (ASD).

Schizophrenia – Suicide is the principal cause of premature death in patients with schizophrenia. Suicidal behaviour is significantly less in patients treated with clozapine or olanzapine.

Cannabis might increase the risk of schizophrenia by 30%.

Brain stimulation techniques

ECT – National Institute of Clinical Excellence (NICE) has recommended that ECT should be used only in patients suffering severe depressive illness, catatonia or a severe or prolonged manic episode, and then only after an adequate trial of other treatments have been ineffective and/or the condition is considered potentially life-threatening.

FDG-PET and Dementia

The distribution of FDG reflects cerebral glucose metabolism.

Diagnosing early Alzheimer's disease can be difficult using traditional clinical criteria and MRI. FDG-PET is able to diagnose early AD by identifying areas of hypometabolism in parietal and temporal regions.

CHAPTER 14

Acute Poisoning

1. DIAGNOSIS OF ACUTE POISONING

History

Circumstantial evidence:

- Suicide note.
- Circumstances under which found, e.g. empty containers, tablets or capsules nearby.

Physical Signs

See Table 1 for the common clusters of diagnostic signs in poisoning.

Table 1: Common clusters of diagnostic signs in poisoning

Feature cluster	*Likely poisons*
• Coma, hypertonia, hyperreflexia extensor plantar responses, myoclonus, strabismus, mydriasis, sinus tachycardia, skin hot and dry	Tricyclic antidepressants; less commonly or phenadrine, thioridazine, antihistamines
• Coma, hypotonia, hyporeflexia, plantar responses flexor or non-elicitable, hypotension	Barbiturates, benzodiazepines and alcohol combinations, severe tricyclic antidepressant poisoning
• Coma, miosis, reduced respiratory rate	Opioid analgesics
• Nausea, vomiting, tinnitus, deafness, sweating, hyperventilation, vasodilatation, metabolic acidosis	Salicylates
• Restlessness, agitation, mydriasis, anxiety, tremor, tachycardia, convulsions, arrhythmias	Sympathomimetics
• Hyperthermia, tachycardia, delirium, agitation, mydriasis	Ecstasy
• Blindness (usually with other features)	Quinine, methanol
• Miosis and hypersalivation	Organophosphorus and carbamate insecticides, nerve agents

Note: Skin blisters are common in poisoned patients, and sufficiently uncommon in patients unconscious from other causes, to be of some diagnostic value.

Diagnostic Trial of Antidotes

- Naloxone for opioid poisoning
- Flumazenil for benzodiazepine

Toxicological investigations

Measurement of concentration of a specific toxin in the blood or toxicological screening of blood or urine can be used to establish a diagnosis of poisoning.

Poisons for which emergency measurement of plasma or serum concentration is essential are listed in Table 2.

Non-toxicological investigations

a. Inspection of blood

- Chocolate-coloured blood suggests methemoglobinaemia caused by drugs such as dapsone, ingestion of nitrates and nitrites.
- Pink plasma suggests hemolytic poisons, e.g. sodium chlorate.
- Brown plasma points to presence of circulating myoglobin secondary to rhabdomyolysis.

Table 2: Measurement of plasma or serum concentration in poisoning

• Carboxyhaemoglobin
• Ethanol (when monitoring treatment in ethylene glycol and methanol poisoning)
• Ethylene glycol
• Iron
• Lithium
• Methanol
• Paracetamol
• Salicylate
• Theophylline

b. Inspection of urine

- Brown discoloration may be due to presence of haemoglobin (if intravascular haemolysis), myoglobin secondary to rhabdomyolysis or metabolites of paracetamol.
- Crystals after overdose with primidone or ingestion of ethylene glycol.

c. *Haematology* is of little diagnostic value, though – prolongation of PT may be secondary to ingestion of anticoagulants or may be due to liver necrosis in paracetamol poisoning.

d. *Biochemistry*: Usefulness of biochemistry in various poisons is depicted in Table 3.

Radiology

It can be used to confirm ingestion of button batteries, or globules of metallic mercury. Sustained release iron salts may show in plain abdominal X-ray.

ECG

Sinus tachycardia with prolonged PR and QRS intervals in an unconscious patient should point to tricyclic antidepressant overdose. Overdosing with cardiac glycosides or potassium salts also induces characteristic ECG changes.

Clinical features and complications of poisoning

Table 3: Usefulness of biochemistry in various poisons

Biochemistry	*Poisoning*
• Serum sodium	Hyponatremia in ecstasy poisoning
• Serum potassium	Hypokalaemia in theophylline poisoning Hyperkalaemia in digoxin poisoning, rhabdomyolysis, haemolysis
• Plasma creatinine	Renal failure in ethylene glycol poisoning
• Blood sugar	Hypoglycemia in insulin poisoning, hypoglycemia and hyperglycemia in salicylate poisoning
• Serum calcium	Hypocalcemia in ethylene glycol poisoning
• Serum ALT and AST	Increased in paracetamol poisoning
• Serum phosphate	Hypophosphatemia in severe paracetamol induced renal tubular damage
• Acid-base disturbances, including metabolic acidosis	Salicylate poisoning
• RBC cholinesterase activity	Organophosphorus insecticide and nerve agent poisoning
• Whole blood methaemoglobin concentration	Nitrite poisoning

The toxicity of a substance, and therefore the features of poisoning can be predicted from:

- Its physiochemical properties
- Its pharmacological/toxicological actions
- The route of exposure
- The dose

2. PRINCIPLES OF MANAGEMENT

A. *Admission to hospital*: If cardiorespiratory depression or other complications.

B. *Reducing absorption*:

REMOVAL OF UNABSORBED POISON

a. *Induced vomiting* – should be attempted only if patient is fully conscious and co-operative; in a drowsy or semiconscious patient there is risk of aspiration into respiratory tract. Contraindicated in corrosive poisoning because of risk of oesophageal rupture. Methods– (a) Ingestion of hypertonic saline solution. (b) Syrup of ipecac – 15 mL by mouth followed by large amounts of water. Although syrup of ipecacuanha is an effective emetic, there is little evidence that its use prevents significant absorption of toxic material.

b. *Gastric lavage* – by nasogastric intubation with nasogastric tube and flushing the stomach with large quantities of fluid.

Indications: (a) Patient drowsy or unconscious. (b) Patient conscious but uncooperative as in suicidal attempt.

Contraindications: (a) Corrosive poisoning because of danger of rupture of oesophagus. (b) Kerosene poisoning because aspiration of even small quantity into respiratory tract may cause pneumonia. Precautions – Gastric lavage is most helpful if performed within 4 hours after ingestion of poison. Due precautions should be taken to prevent aspiration in unconscious patient such as head low position, turning the head to one side and suction of nasopharynx after the procedure. Lavage fluid – Warm water serves the purpose, in babies saline. Special solution should be used in opium poisoning (potassium permanganate), glutethimide (castor oil), and iron poisoning (desferrioxamine). After lavage all fluid should be removed except in iron poisoning.

c. *Adsorbents* – must be administered within one hour of ingestion of the poison. Refined, activated charcoal single doses of 25–100 g by mouth prevents significant absorption of many drugs (e.g. aminophylline, aspirin,

carbamazepine, digoxin, paracetamol, phenobarbital, phenytoin, theophylline).

Toxins poorly absorbed by activated charcoal are acids and alkalis, cyanide, ethanol, ethylene glycol, iron, lithium and methanol.

d. *Whole bowel wash* – with normal saline or polyethylene glycol electrolyte solutions, can serve the same purpose as cathartics. Whole bowel irrigation may be considered following potentially toxic ingestion of sustained-release or enteric-coated drugs.

FURTHER MANAGEMENT

Hypothermia: A core temperature below 35°C, measured in the rectum or ear, may be recorded in deeply unconscious patients who have been exposed, particularly in cold weather, for several hours. Hypothermia is best treated by placing the patient in room with moistened air at a temperature of 27–29°C and covering him or her with a foil space blanket to minimize heat loss. Local radiant heat should not be used.

Convulsions: Caused by, for example, tricyclic antidepressant drugs can usually be controlled with intravenous diazepam, once hypoxaemia and acidosis have been corrected. Rarely, muscle relaxation and mechanical ventilation are required, together with an anti-epileptic drug such as phenytoin.

Fluid, acid-base and electrolyte balance: Patients who are vomiting should be given fluids intravenously to replace gastrointestinal losses. Severe and clinically significant hypokalaemia (e.g. that caused by theophylline or β2-agoinst poisoning) should be corrected by infusing potassium to prevent arrhythmias.

Metabolic acidosis is a common complication of many poisons (Table 4) and, after correction of hypoxia, infusion of sodium bicarbonate may be necessary. Hypoglycemia may follow an overdose of insulin, sulphonylureas or ethanol, and may occur in paracetamol-induced liver failure. It is corrected by infusing 10% dextrose, if necessary, after a bolus injection of 50% dextrose, 50 mL.

Table 4: Toxins causing metabolic acidosis

• Carbon monoxide
• Cyanide
• Ethylene glycol
• Iron salts
• Isoniazid
• Methanol
• Salicylate
• Paracetamol
• Tricyclic antidepressants

Hypertension: A few drugs (e.g. monoamine oxidase inhibitors) when taken in overdose may produce severe systemic hypertension, and there may be risk of arterial rupture, particularly intracranially. To prevent this, an α-adrenergic blocking agent (e.g. phentolamine, 5–60 mg i.v. over 10–30 minutes) should be administered.

Pain: Patients who have ingested a corrosive substance usually suffer severe pain, which can be relieved with an opioid.

Nursing care: Unconscious patients should be turned from side to side at least every 2 hours. Bullous lesions should be left intact until they burst, to reduce the risk of infection. De-roofing should be performed when the blister bursts; a non-adhesive dressing is then applied.

C. *Increasing elimination*:

Urine alkalization – increases elimination of salicylates, phenoxyacetate herbicides, phenobarbitone and barbitone. Alkalinization of urine is more important than a large i.v. fluid load. A diuresis of more than 500 mL/h for long periods may be harmful.

However, with exception of salicylate poisoning, urine alkalization is the first-line monotherapy for poisoning with these agents. Before commencing urine alkalization, it is important to correct plasma volume depletion, electrolytes (administration of sodium bicarbonate exacerbates pre-existing hypokalaemia) and metabolic abnormalities.

Multiple-dose activated charcoal: Use of MDAC involves repeated administration of oral activated charcoal to increase elimination of drug that has already been absorbed into the body. Elimination of drugs with small volume of distribution (<1 litre/kg), low pKA (which maximizes transport across membranes), low binding affinity and prolonged elimination half-life following overdose is particularly likely to be enhanced by MDAC (Table 5). MDAC also improves total body clearance of the drug when endogenous processes are compromised by liver and/or renal function.

Table 5: Drugs whose elimination is increased by MDAC

• Carbamazepine
• Quinine
• Dapsone
• Theophylline
• Phenobarbital

Dose: Initial 50–100 g and then at a rate not less than 12.5 g/hr, preferably via nasogastric tube. Smaller initial doses (10-25 g) can be used in children. If the patient has ingested a drug that induces vomiting (e.g. theophylline), i.v. ondansetron is effective as an emetic and thus enables administration of MDAC.

Haemodialysis and haemoperfusion – are indicated for patients with a combination of severe clinical features and high plasma toxin concentrations. Haemodialysis enhances elimination of salicylate, lithium, methanol, isopropanol, ethylene glycol and ethanol. Haemoperfusion effectively removes barbiturates, carbamazepine, disopyramide, ethchlorvynol, glutethimide, meprobamate, methaqualone, theophylline and trichloroethanol derivatives. However, MDAC is as effective as haemoperfusion in phenobarbitone, carbamazepine and theophylline poisoning and is easier to use.

D. *Antidotes*: Table 6 lists antidotes used to treat poisoning that may be lifesaving in patients with certain types of poisoning. Mechanism of action – (a) *Inert complex formation* – e.g. chelating agents for heavy metal poisoning, cyanide antidotes, Prussian blue. (b) *Accelerated detoxification* – e.g. thiosulphate for cyanide poisoning. (c) *Reduced conversion to more toxic compound* – e.g. ethanol fomepizole. (d) *Competition for essential receptor sites* – e.g. Oxygen in CO_2 poisoning, naloxone in opiate poisoning, vitamin K for oral anticoagulants. (e) Blockade of receptor sites – Atropine and pralidoxime for anticholinesterase poisoning. (f) Bypassing the effects of the poison – e.g. oxygen in cyanide poisoning, glucagon in b-blocker poisoning.

Table 6: Antidotes used to treat poisoning

Poison	*Antidote*
• Aluminium	Deferoxamine (desferrioxamine)
• Arsenic	Dimercaprol (BAL), DMSA
• Benzodiazepines	Flumazenil
• β-adrenoceptor blocking drugs	Atropine, glucagon
• Copper	D-penicillamine, DMPS
• Cyanide	Oxygen, dicobalt edetate, hydroxocobalamin, sodium nitrite, sodium thiosulphate
• Digoxin and digitoxin	Digoxin-specific antibody fragments
• Ethylene glycol	Ethanol, fomepizole
• Iron salts	Deferoxamine (desferrioxamine)
• Lead (inorganic)	Sodium calcium edetate, DMSA
• Methaemoglobinaemia	Methylthioninium chloride (methylene blue)
• Methanol	Ethanol, fomepizole
• Mercury (inorganic)	DMPS
• Opioids	Naloxone
• Organophosphorus insecticides	Atropine, pralidoxime
• Paracetamol	N-acetylcysteine
• Thallium	Prussian (Berlin) blue
• Warfarin and other anticoagulants	Vitamin K_1

E. *Maintenance of vital function*:
Respiration: (a) *Maintenance of patent airway* – by repeated suction of throat and nasopharynx. Preventing tongue from falling back by pulling the jaw forwards or use of J-shaped metallic airway. Endobronchial suction if profuse secretions, or collapse of lobe or lung segment from bronchial obstruction. Tracheostomy if prolonged coma with profuse secretions or in cases requiring assisted mechanical respiration. (b) *Mechanical respiratory support* – for medullary or peripheral neuromuscular paralysis as in barbiturate, opium and organophosphorus poisoning. Ambu's bag can be used if respirator is not available, when artificial respiration is required only for a short time, or in case of emergency. (c) *Oxygen* – by intranasal catheter or mask.

F. *Medicolegal responsibilities of attending physician:* (a) Samples of gastric content should be saved for chemical analysis. (b) Immediate information to the police. (c) In case of death due to poisoning, autopsy must be performed and blood samples and viscera sent to chemical analyser.

G. *Psychiatric and social problems* – need appropriate management.

3. POISONING WITH PESTICIDES

ORGANOPHOSPHATE AND CARBAMATE POISONING

Clinical Features

Combination of nicotinic and muscarinic effects (acetylcholine excess Table 7).

Investigations

Diagnosis can be confirmed by measurement of plasma (normal 100–250 U/mL) and, preferably, erythrocyte cholinesterase activity (Normal 150–300 U/mL). Moderate poisoning is often associated with reduction of enzyme activity to 10–20% of normal value, severe poisoning to less than 10%. Other investigations include liver and kidney function tests, ECG, X-ray chest, arterial blood gas analysis.

Table 7: Action of acetylcholine and effects of organophosphate poisoning

Site of action	*Physiologic effects*
• *Muscarinic effects*	
– Sweat glands	Sweating
– Pupils	Constricted pupils
– Lacrimal glands	Lacrimation
– Bronchial tree	Wheezing
– GI tract	Cramps, vomiting, diarrhoea, tenesmus
– Cardiovascular	Bradycardia, fall of BP
– Ciliary body	Blurred vision
– Bladder	Urinary incontinence
• *Nicotinic effects*	
– Striated muscle	Fasciculations, cramps, weakness, paralysis, respiratory distress, cyanosis
– Sympathetic ganglia	Tachycardia, elevated BP
• *CNS effects*	Anxiety, restlessness, ataxia, convulsions, coma

Factors associated with increased mortality:

1. Increased time delay in initial atropinisation
2. Higher dosage of PAM in first 24 hours
3. Respiratory paralysis at time of admission
4. Development of intermediate syndrome

Management

1. *Removal of unabsorbed poison*: Gastric lavage with 1–3% potassium permanganate or 0.5% soda bicarb.
2. *Administration of antidotes*:
   a. *Atropine* – 2 mg slowly i.v. (child 0.02 mg/kg) every 5 minutes till the pupils start to dilate. As much as 50–100 mg may be needed in severe cases. Once the pupils dilate atropine is stopped. If over a period of few hours the pupils again constrict, further atropine is required. Patient should be well oxygenated while on atropine as it may precipitate ventricular fibrillation in presence of hypoxia. Atropine can also be administered as continuous drip 150 mg in 250 mL 5% dextrose 6 hrly for 24 hrs. Atropine has no effect on respiratory paralysis. Ventilatory support is necessary. PEEP may be used in presence of pulmonary oedema, once circulation and BP have been stabilized.
   b. *Oximes* – are choline esterase inhibitors and can be given simultaneously with atropine or as soon as possible after atropine. Effects of the drugs are most prominent at skeletal neuromuscular junctions and muscle weakness and fasciculation should improve within 30 minutes.
      i. Pralidoxime (PAM) Dose – 30 mg/kg IV at rate not exceeding 500 mg/minute, or IM every 4 hours for 24 hours.
      ii. Obidoxime 3–6 mg/kg IV 4-hourly for 24 hours.
3. *Diazepam*: Early addition of diazepam 5–10 mg IM or IV not only affords further protection against occurrence of seizures, but also diminishes the severity of muscle twitching.
4. *Management of complications*:
   Acute complications – (a) Pulmonary oedema – (i) Suction of throat and nasopharynx to remove froth and maintain patent airway. (ii) Oxygen. (iii) IV atropine till appearance of signs of adequate atropinisation in order to reduce bronchial secretions. (iv) IV Frusemide 60–80 mg. (b) Respiratory paralysis – May occur in acute stage due to severe poisoning or as a delayed complication after initial period of improvement often associated or preceded by palatal paralysis and facial palsy. It can be detected early by measuring chest expansion at frequent intervals. Intermittent positive pressure respiration is used. Antibiotic cover to prevent bronchopneumonia. (c) Medullary paralysis – Fluctuations in pulse rate and blood pressure. Cardiac arrhythmias and profound hypotension may occur in terminal stages.

Delayed Complications

Intermediate syndrome (Type II paralysis) – occurs in 5–10% of patients 1–4 days after acute poisoning. Features include proximal and neck muscle weakness and dysphagia in absence of muscarinic signs. It reverses in 4–18 days. Atropine, PAM have no effect on this syndrome.

Delayed neuropathy – TOCP (Triorthocresyl- phosphate) and TCP (Tricresyl phosphate) particularly produce delayed neurotoxicity. It appears 9–20 days after ingestion, with no initial signs of acute poisoning. There is a pure motor distal axonal degeneration neuropathy and no sensory loss. Recovery is slow.

ALUMINIUM PHOSPHIDE (ALP)

If is used as a grain preservative.

Clinical Features

Garlicky taste and smell, retrosternal burning, epigastric discomfort and recurrent vomiting. Tremors and drowsiness. Liberated phosgene gas causes dyspnoea, pulmonary oedema, bradycardia and circulatory collapse. ARDS develops if patient survives for 12–24 hrs. Activated charcoal 90 g to absorb PH_3 from GI tract. Further absorption is reduced by administration of antacids and H_2 receptor antagonists. Medicated liquid paraffin hastens its elimination.

Investigations

(a) Positive silver nitrate test in gastric aspirate or expired air. (b) ECG – Changes secondary to toxic myocarditis.

Management

No specific antidote. Clothing if soiled with vomitus should be removed, affected parts washed with soap and water. GL with 3–5% sodium bicarbonate solution which minimises conversion to phosphine. Supportive measures – Glucose saline, corticosteroids, dopamine.

PARAQUAT

Clinical Features

Initial features of poisoning include nausea, vomiting and diarrhoea, but very large doses may cause death from coma, metabolic acidosis, pulmonary oedema and myocardial depression within a few hours. Those who survive for 3–4 days have severe painful ulceration of lips, tongue, pharynx, and larynx with dysphagia, cough, dysphonia and inability to clear saliva and other secretions. Acute renal failure is common. Increasing breathlessness and pulmonary oedema herald almost certain death within a few days or weeks, as extensive pulmonary fibrosis develops.

Management

Empty the stomach and give AC. Pharmacological interventions are not effective and if plasma concentration indicates a fatal outcome, it is best to keep the patient comfortable.

THALLIUM

Thallium salts are used in some rodent poisons, fireworks, imitation jewellery. Most cases occur after oral ingestion or inhalation of fumes.

Cl. Fs. Painful peripheral neuropathy and alopecia are two cardinal symptoms. Other associated symptoms are GI and cardiac problems which appear early. Ataxia, tremor, athetosis, cranial nerve palsy and rarely convulsions and coma.

Tr. Prussian blue (potassium ferric ferrocyanide) or potassium as potassium chloride.

PHENOXYACETATE HERBICIDES

Clinical features include burning sensation in mouth and throat, nausea and vomiting, sweating, hyperventilation, convulsions and coma. Acute myositis with pain, fasciculation, myotonia, weakness and myoglobinuria have been reported.

Management: Supportive measures, induction of isotonic sodium bicarbonate to raise urine pH to as close to 8 as possible.

Anticoagulants – are used as rodenticides.

Clinical features: Symptoms are unlikely after accidental ingestion, because very large amounts have to be eaten to ingest a significant amount of anticoagulant to cause haemorrhagic complications.

Management: Vitamin K until clotting returns to normal. For severe acute cases whole blood, fresh frozen plasma or clotting factor concentrates may be required.

4. PETROLEUM DISTILLATES

Kerosene, white spirit

Clinical features: Nausea, vomiting and diarrhoea. If ingestion of large quantity, CNS effects – initial excitation followed by impaired consciousness. Aspiration into respiratory tract may result in haemorrhagic pneumonitis with breathlessness, wheezing and cyanosis. Convulsions and intravascular haemolysis may occur occasionally.

Investigations: (a) WBC count. (b) X-ray chest – 6 hours after ingestion, no change before that.

Management: (a) Hospitalize. Ascertain amount, vomiting (because of danger of aspiration), whether any drug ingestion, and respiratory distress. (b) Emptying of stomach and lavage if quantity taken is large. Prior protection of lungs by cuffed endotracheal tube is essential as emesis and lavage may lead to aspiration of the poison. Pinch lavage tube while withdrawing to prevent aspiration. (c) Liquid paraffin – Absorption of ingested kerosene can be slowed down by giving liquid paraffin 250 mL orally. (d) Supportive measures. (e) Corticosteroids and antibiotics only if lipid pneumonitis.

Sequelae: (a) Persistent cough. (b) Pneumatocoele with danger of pneumothorax 4–6 weeks later.

5. POISONING WITH PSYCHOTROPIC DRUGS

ANXIOLYTICS

Barbiturates

Clinical features: Impairment of consciousness, varying from drowsiness to deep coma, hypotonia of limbs, depression of deep reflexes. Plantars may be extensor. Depression of vital centres produces: Respiratory paralysis and hypotension. Hypothermia, shock and anuria may occur. Bullous rash on skin especially on pressure points is characteristic but not diagnostic.

Management

Assessment of patient: According to depth of unconsciousness, presence of respiratory depression, hypotension, hypothermia and shock; presence of anuria, type of barbiturate and the amount consumed, duration of time between ingestion of poison and hospitalisation, and estimation of blood barbiturate levels.

Management of the poisoning:

1. *Removal of absorbed poison* – by induced vomiting or gastric lavage. Nasogastric intubation is required in most cases since patient is unconscious.
2. *Removal of absorbed poison*:
   a. *Alkaline diuresis* – has already been described.
   b. *Haemodialysis* – advantages are faster elimination of the poison and its effectiveness even in case of short and intermediate acting barbiturates. Indications – (i) Severe poisoning with deep coma and depression of vital centres. (ii) Blood barbiturate level is high to begin with (10 mg/100 mL or more) or continues to rise under observation. (iii) Patient fails to improve or deteriorates Inspite of forced diuresis. (iv) Presence of renal disease. Contraindications – Presence of bleeding piles or peptic ulcer which contraindicates anticoagulation. As patient improves after dialysis or forced diuresis, a close watch must be kept for next few days as re-excretion into the circulation of the poison bound to tissue proteins may cause a relapse.

Benzodiazepines

(diazepam, alprazolam, lorazepam, etc.).

Clinical features: Most important is CNS depression. Occasionally, this may be sufficient to cause respiratory insufficiency, particularly in those with pre-existing chest disease such as chronic bronchitis. Usually, the onset of coma is progressive, but patients may experience symptoms such as confusion, dizziness, nystagmus, ataxia and dysarthria prior to coma. BP may fall with increasing coma.

Management: Nursing and supportive care. Mechanical ventilation may be necessary. Flumazenil, a specific antagonist may be given in severe cases (coma, hypotension or respiratory depression). Dose 0.5 mg i.v. over 1 minute, the same dose being repeated if there is no response or only a partial response, or i.v. infusion 0.1–0.5 mg/hr. If used when tricyclic antidepressants have been taken together with benzodiazepines, it may precipitate convulsions and cardiac arrhythmias.

Note: Full recovery may take several days. Patients habituated to benzodiazepines may develop withdrawal symptoms, including acute psychoses and fits.

Non-benzodiazepines (Buspirone, chlormezanone, meprobamate).

Clinical features: Symptoms similar to benzodiazepines. Meprobamate is most toxic of the group, causing hypotension, hypothermia, coma with respiratory depression and occasionally pulmonary oedema. Treatment is supportive, but haemoperfusion may be at times necessary.

ANTIDEPRESSANTS

Tricyclic antidepressants (imipramine, amitriptyline, doxepin, clomipramine)

Clinical features: Diagnostic triad of coma, convulsions and cardiac arrhythmias. Initially symptoms are related to anticholinergic actions – dry mouth, blurred vision, sinus tachycardia and drowsiness. *Additional features* of severe poisoning include hypotension, respiratory depression, hyperpyrexia, hypothermia, delirium (more often during recovery), hypertonia, hyperreflexia, extensor plantar responses, ileus and retention of urine. Tachyarrhythmias may occur as also skin blisters. The severity of poisoning can be assessed from QRS interval on ECG and plasma drug concentration. QRS >0.11 seconds and plasma concentration >1000 mg/litre usually indicate serious toxicity.

Management: 1. *Gastric lavage* – of activated charcoal 50–200 g into the stomach. 2. *Supportive measures* – (a) Correction of acidosis. (b) Arrhythmias treated with sodium bicarbonate even in patients who are not acidotic. Unless cardiac output is significantly compromised, antiarrhythmic drugs are not used because they aggravate adverse effects of tricyclics on the myocardium. (c) Adequate oxygenation. (d) Maintenance of normal plasma potassium level and correction of acidosis. 3. *Treatment of convulsions* – with diazepam 5–20 mg IV.

Antipsychotics: (Phenothiazines, butyrophenones, thioxanthenes)

Clinical features: (a) Extrapyramidal reactions–dystonia, dyskinesia, akathisia. (b) General features – Depression of consciousness, hypotension, respiratory depression, hypothermia. ECG changes and arrhythmias, fits. (c) Neuroleptic malignant syndrome – Hyperthermia, fluctuating consciousness, muscular rigidity, autonomic dysfunction (see Table 8).

Management: (a) Supportive measures. (b) Treatment of arrhythmias. (c) Specific measures for extrapyramidal reactions.

Table 8: Specific measures for extrapyramidal reactions in antipsychotic poisoning

Disorder	*Clinical features*	*Treatment*
Dystonic reaction	Involuntary m. contraction (face and jaw). Oculogyric crisis	Benztropine 1–2 mg IM or IV. Diazepam 10 mg IV
Akathisia	Subjective motor restlessness and continual pacing	Reduce dose of neuroleptic Benztropine 1–6 mg/day Diazepam 10–30 mg/day Propranolol 40–120 mg/day
Parkinsonism	Rigidity, bradykinesia, tremor	Reduce dose of neuroleptic Benztropine 1–6 mg/day
Tardive dyskinesia (late onset)	Choreoathetoid movements (tongue, lips, jaw)	Withdraw neuroleptic Tetrabenazine Sulpiride Ca channel blocker
Neuroleptic malignant syndrome	Fever, muscular rigidity, coma and death	Discontinue neuroleptic ICU support Bromocriptine Dantrolene

SELECTIVE SEROTONIN-RE-UPTAKE INHIBITORS

Clinical features: Nausea, vomiting, agitation and tachycardia. Convulsions may develop over large overdoses (>1.5 g). Patients who have taken SSRIs in combination with drugs with serotoninergic effect (e.g. tryptophan) or an MAOI are at risk of restlessness, hyperpyrexia, rhabdomyolysis and renal failure.

Management: Supportive and symptomatic. Use of dantrolene to reduce muscle spasm, or paralysis and ventilation may be required in severe cases.

MONOAMINE OXIDASE INHIBITORS

Clinical features: CNS and autonomic dysfunction, agitation, abnormal movements, hyper-reflexia, muscular rigidity, convulsions, sweating, hyperpyrexia, hyperventilation, tachycardia, hypertension or hypotension, urinary retention, coma.

Management: Parenteral diazepam or chlorpromazine to control agitation, ventilation if respiratory embarrassment caused by muscle spasm; dantrolene may reduce spasm.

6. POISONING BY ALCOHOLS

ETHANOL

Clinical features: Smell of alcohol.

Mild intoxication: Rowdiness, disorientation, irrelevant talk, incoordination.

Moderate intoxication: Unconsciousness, hypotonia, depressed jerks. Pupils normal or slightly dilated.

Severe intoxication: Deep coma, loss of jerks, extensor plantars, dilated pupils, irregular breathing. Death from medullary paralysis.

Management

1. *Removal of unabsorbed poison* – by gastric lavage.
2. *Correction of hypoglycemia* – with 50 mL 50% glucose IV. Blood should be collected for sugar estimation before giving glucose. In mild intoxication, further treatment is not necessary. In moderate to severe intoxication, patient may continue to remain drowsy for 4–6 hours and 5% glucose drip should be continued with high doses of vitamin B complex.
3. *Mannitol* – 350 mL of 20% solution IV if patient fails to improve.
4. *If patient continues to be comatose* – the possibilities are – (a) Mixed poisoning – such as simultaneous ingestion of alcohol and barbiturates or other narcotics. (b) Head injury – due to fall. Lumbar puncture should be done to rule out subarachnoid haemorrhage. (c) Hepatic coma – may be precipitated in a chronic alcoholic with liver cell failure by a bout of alcohol.
5. *Contamination of alcohol with methyl alcohol* – Metabolism of methyl alcohol in the body results in the formation of toxic products like formaldehyde and formic acid. Clinical manifestations are dimness of vision (irreversible blindness in severe cases), acidotic breathing, altered state of consciousness, convulsions, coma and death. Management – Treatment of acidosis by IV sodabicarb., IV glucose, and general supportive treatment. Haemodialysis can be lifesaving in severe cases.
6. *Delirium tremens* – may develop in patients addicted to alcohol on recovering from the acute intoxication due to withdrawal. It is characterised by restlessness, tremors, confusion, irrelevant talk. Treatment – IV glucose, high doses of vitamin B complex and sedatives.
7. *Treatment of associated complications* – Broad spectrum antibiotics for pneumonia, antacids and bland diet for gastritis.

ETHYLENE GLYCOL

Is most commonly used as an antifreeze. It may be drunk accidentally by children, or by adults as a substitute for ethanol.

Clinical features: See Table 9.

Table 9: Clinical features of ethylene glycol poisoning
Stage 1 (30 mins. to 12 hrs) – GI and nervous system involvement
• Nausea, vomiting, hematemesis
• Coma and convulsions (often local)
• Nystagmus, ophthalmoplegia, papilloedema, depressed reflexes, myoclonic jerks, tetanic contractions
• Vth, VIIth, VIIIth nerve palsies
Stage 2 (12–24 hrs) – Cardiorespiratory involvement
• Tachypnoea
• Tachycardia
• Mild hypertension
• Pulmonary oedema
• Congestive cardiac failure
Stage 3 (24–72 hrs)
• Flank pain
• Renal angle tenderness
• Acute tubular necrosis

Management

Treatment of cardiorespiratory depression and correction of metabolic acidosis and hypocalcemia. Ethanol 50 g p.o. given immediately (e.g. 125 mL gin, whisky or vodka), followed by further oral doses or i.v. infusion of 10–12 g ethanol/hr to achieve a blood ethanol concentration of 500–1000 mg/L. Dose may be increased to 17–22 g/hr if haemodialysis is undertaken, because ethanol is dialysable.

Fomepizole is another alternative antidote. Loading dose 15 mg/kg over 30 mins., followed by four 12-hrly doses of 10 mg/kg until ethylene glycol concentration is <200 mg/L. If haemodialysis is used, frequency of dosing should be increased to 4 hrly during dialysis because fomepizole is dialysable.

METHANOL

Methanol is found in antifreeze solutions, wind-screen washing fluid, paint removers, varnishes and shoe polish and is widely used as a solvent and to denature ethanol.

Clinical features: When ingested it causes mild and transient inebriation, nausea, vomiting, abdominal pain mild CNS depression. This is followed by a latent period of 12–24 hrs, after which uncompensated metabolic acidosis develops, coma supervenes and visual function becomes impaired; this ranges from blurred vision and altered visual fields to complete blindness. Mortality increases with the severity and duration of metabolic acidosis. Patients who survive may suffer permanent blindness, rigidity, hypokinesis and other parkinsonian-like signs.

Management: Ethanol delays metabolism of methyl alcohol to its toxic metabolites by competing for alcohol dehydrogenase.

Dose: Loading dose – (a) IV - 7.6-10 mL/kg of 10% solution in dextrose. (b) Oral - 1 mL/kg of 95% ethanol in orange juice.

Fomepizole is a direct alcohol dehydrogenase antagonist. Steroids: Retrobulbar injection of triamcinolone could salvage vision in patients having retinal toxicity since retinal toxicity is due to accumulation of toxic metabolites of methanol, treatment with folic acid and haemodialysis cause removal of these products.

Haemodialysis. Indications – (a) Persistent refractory high ion gap metabolic acidosis, visual and mental obtundation, > 30 mL of methyl alcohol ingestion or > 50 mg/dL blood levels, deteriorating vital signs despite intensive supportive care, kidney failure or significant electrolyte disturbances unresponsive to conventional therapy.

If appropriate, ethanol is continued until methanol is undetected in the blood.

7. ANTICONVULSANTS

CARBAMAZEPINE

Cl. Fs: Anticholinergic features (dry mouth, coma, convulsions). Also drowsiness, nystagmus, ataxia and incoordination are often observed. Pupils may be dilated and divergent squint may be present.

Hallucinations may occur, particularly in the recovery phase.

Mn: Initial single dose of 50–100 g activated charcoal reduces absorption, followed by MDAC 12.5 g/hr to increase elimination.

PHENYTOIN

Cl Fs: Nystagmus, dysarthria, ataxia, drowsiness and coma.

Mn: Single dose of AC 50–100 g will reduce absorption. MDAC will increase phenytoin elimination.

SODIUM VALPROATE

Cl. Fs: Fever, muscle spasms, hypocalcemia, coma, liver damage and thrombocytopenia. Drowsiness is common, and toxic encephalopathy and optic atrophy have been described. Cerebral oedema is uncommon and is not dose-related.

Mn: Supportive measures including correction of electrolyte and metabolic abnormalities. Neither MDAC nor dialysis increases elimination.

8. ANALGESIC POISONING

NON-NARCOTIC ANALGESICS

Salicylates and Aspirin

Cl. Fs. of salicylism in adults.

Mild to moderate intoxication (plasma concentration <700 mg/L) – Deafness, tinnitus, nausea, vomiting, hyperventilation, sweating, vasodilatation, tachycardia, respiratory alkalosis, metabolic acidosis.

Severe intoxication (plasma concentration >700 mg/L) – All symptoms of less severe poisoning plus confusion, delirium, hypotension, cardiac arrest, academia.

Less common complications: Pulmonary oedema, cerebral oedema, convulsions, coma, encephalopathy, renal failure, tetany, hyperpyrexia, hypoglycemia.

Biochemical alterations: (a) Respiratory alkalosis due to stimulation of respiratory centre, hyperpnoea and washing out of CO_2. (b) Hypokalaemia. (c) Hyperglycemia. (d) Metabolic acidosis. (e) Hypoprothrombinaemia.

Mn. (a) MDAC 50–100 g followed by 50 g q4h, (or 12.5 g/hr) until recovery. (b) Antacids e.g. aluminium hydroxide and milk q2h p.o. or by slow intragastric drip. (c) Correction of dehydration, electrolyte imbalance and metabolic acidosis. (d) Urine alkalization (pH 7.5–8.5) by giving 225 mL of 8.4% sodium bicarbonate. Hypokalaemia should be corrected before giving sodium bicarbonate, because it lowers serum potassium concentration further.

Paracetamol

Cl. Fs. – of severe paracetamol poisoning – (a) Nausea and vomiting. (b) Upper abdominal pain and hepatic tenderness. (c) Fulminant hepatic failure on third to sixth day, encephalopathy, cerebral oedema, hyperventilation, hypoglycemia, acidosis, hemorrhage, renal failure.

Hypophosphatemia may contribute to morbidity and mortality by inducing mental confusion, irritability, coma and abnormalities of platelet, RBC and WBC function. Phosphaturia appears to be the principal cause of hyperphosphatemia. It may occur in absence of fulminant hepatic failure and indicates paracetamol-induced renal tubular damage.

Biochemical abnormalities: (a) Metabolic acidosis and lactic academia initially. (b) Abnormal liver function tests with marked rise in aminotransferase. (c) Prolongation of prothrombin time. (d) Hyperbilirubinemia.

Management

See Table 10 for the management of paracetamol poisoning.

Table 10: Management of paracetamol poisoning.

Antidote	*Dosage schedule*	*Total dose*
N-acetylcysteine (i.v.)	150 mg/kg in 5% dextrose, 200 mL over 15 minutes, 50 mg/kg in 5% dextrose 500 mL over next 4 hrs and 100 mg/kg in 5% dextrose 1000 mL over next 16 hrs.	Total dose 300 mg/kg over 20¼ hrs.
N-acetylcysteine (oral)	140 mg/kg initially, then 4-hrly doses of 60 mg/kg.	Total dose 1330 mg/kg over 72 hrs.
Methionine (oral)	2.5 g initially, then three 4-hrly doses of 2.5 g.	Total dose 10 g over 12 hrs.

NARCOTIC ANALGESICS

Opioids (morphine, diamorphine, codeine, methadone, tramadol, dextropropoxyphene, buprenorphine).

Clinical Features

Pin point pupils, respiratory depression, cyanosis, hypothermia, hypotension, coma. Other complications include convulsions, cardiac arrhythmias and conduction defects, pulmonary oedema, renal failure and rhabdomyolysis.

Management

1. *Clearing the airway* and positioning the patient correctly to minimize risk of aspiration.
2. *Gastric lavage*: Dilute potassium permanganate solution is used and lavage continued till the returning fluid is of the same colour.
3. *Antidotes*: Naloxone – Dose required for full reversal of narcotic effects depends on the drug taken and severity of intoxication, e.g. very large doses may be required for pentazocine. IV naloxone acts immediately and often there is overreaction with hyperventilation, maximal pupillary dilatation, muscle tremor, rise of BP Usual dose 0.4–1.2 mg IV (or less satisfactorily IM) to total dose of 2 mg. The dose may be repeated if pupillary constriction and respiratory depression are not reversed within 1–2 minutes. Graded administration of naloxone is safer than sudden complete reversal.
4. *Supportive treatment*: IV fluids, maintenance of BP and of temperature.
5. *Assisted respiration* – in case of severe respiratory depression not responsive to above measures.

9. POISONING WITH CARDIORESPIRATORY DRUGS

CARDIAC DRUGS

β-blockers

Clinical features: With a large overdose, coma, convulsions (particularly with propranolol), profound bradycardia and hypotension. Respiratory depression and cardiac arrest can also occur. ECG changes include first degree heart block, widening of QRS complex and disappearance of P waves, and prolonged QT interval.

Management: (a) Gastric lavage if ingestion less than 4 hours. Atropine 0.6–1.2 mg will prevent vagal induced cardiovascular collapse during the procedure. (b) Activated charcoal. (c) Glucagon for severe hypotension. Bolus dose of 50–150 mg/kg, followed by infusion of 1–5 mg/hour. A temporary transvenous pacemaker may be necessary.

Digoxin

Cl. Fs.

a. *GI tract* – Anorexia, nausea, vomiting, abdominal pain, diarrhoea, dysphagia.
b. *Cardiac* – Atrial tachycardia, flutter or fibrillation; ventricular ectopics, tachycardia or fibrillation; A-V block; A-V dissociation.
c. *CNS* – Malaise, fatigue, stupor, coma, delirium, hallucinations, headache, seizures, photophobia, transient blindness or scotomata, disturbances of colour vision (green-yellow).

Investigations: (a) ECG – Arrhythmias, changes of hyperkalaemia (in acute overdose): ST-T wave changes; decreased QT interval. (b) Serum K – Increased in acute overdose, decreased or normal in chronic overdose. (c) Serum digoxin – High in acute overdose (>10 µg/litre if severe toxicity).

Assessment of severity: Urgent ECG and electrolytes (particularly magnesium and potassium) and digoxin concentrations. In acute digoxin toxicity, potassium levels > 5 mmol/L are predictive of major toxicity.

Treatment: (a) AC if more than 0.1 mg/kg has been ingested less than 2 hrs previously. (b) Endotracheal intubation and gastric lavage can lead to increased tone and worsen bradyarrhythmia, and premedication with atropine is necessary it these are undertaken. (c) Cardiac monitoring and IV access if ingestion of significant amounts. Normal saline is i.v. fluid of choice, glucose may worsen hypokalaemia. (d) Correction of hypokalaemia and hypomagnesemia.

Table 11: Indications for digoxin antibody fragments

Any of the following:
• Life-threatening dysrhythmias Ventricular tachycardia/ventricular fibrillation Third-degree heart block
• Cardiac compromise in those with underlying cardiac disease
• Serum potassium > 6 mmol/L Digoxin >7.8 µg/6 hrs after acute overdose or in chronic toxicity

Digoxin Fab: These digoxin specific antibodies bind rapidly to digoxin, removing it from the Na^+/K^+ -ATPase pump. Digoxin Fab binds to digoxin in 1:1 ratio; thus the dose required depends on the amount of digoxin to be neutralized (Table 11).

Calculation of Digoxin Fab Dose

From dose ingested: One 40 mg vial of digoxin Fab binds 0.6 mg of digoxin; thus if ingestion of 3 mg requires 6 vials.

From serum digoxin concentration: This method uses the estimated volume of distribution (adults 8 litres/kg, children 13 L/kg) and measured digoxin concentration. Total body burden of digoxin concentration in µg/L (nmol/l × 1.28) × weight (kg) × volume of distribution. Number of 40 mg vials of digoxin Fab required = total body burden/0.6.

By titration: Digoxin Fab dose may be titrated against clinical response; 4–6 vials of digoxin Fab are given and further vials administered depending on their clinical effect. This method may be more useful in patients with hyperkalaemia or heart block than in those with ventricular tachyarrhythmias, in whom treatment is more urgent.

Magnesium enhances Na^+/K^+ - ATPase activity without altering digoxin concentration or digoxin binding. It may be useful when digoxin Fab are indicated but not immediately available. The calcium channel blocking properties of magnesium make it useful in tachyarrhythmias.

Other drugs: Atropine 1 mg i.v. repeated as necessary to all patients with bradyarrhythmia. If other antiarrhythmic drugs are required, class 1B drugs should be used because they do not impair AV nodal conduction. Class 1A drugs are contraindicated.

Temporary pacing may be required in some patients.
Mn: (a) Supportive care. (b) Calcium gluconate 10–20 mL 10% solution IV may reverse prolonged intracardiac conduction defects. (c) Dobutamine 5–40 µg/kg/minute or isoprenaline 5–50 µg/minute IV may be needed to maintain cardiac output.

Calcium-channel blockers (Verapamil, diltiazem, amlodipine, nifedipine).

Cl. Fs: (a) *Cardiac*: Hypotension results from combination of vasodilatation, heart block and myocardial depression. It follows few hours after ingestion of a standard preparation, but may be delayed for up to 18–24 hours with controlled release preparations. Both cardiac and non-cardiac pulmonary oedema can occur. Higher degrees of heart block are common with verapamil and diltiazem. (b) *GI*: Nausea and vomiting. The effect of CCBs on the gut can lead to ileus formation. (c) *Other effects* are seldom life-threatening and include hyperglycemia, lactic acidosis and do not occur in absence of significant cardiac effects.

ACE INHIBITORS

Cl. Fs: GI symptoms (anorexia, nausea, abdominal discomfort) predominate initially, and are followed by headache and paraesthesias. Hypotension, sinus tachycardia, bronchospasm and hyperkalaemia may then develop.

Mn: (a) GL if seen within 1 hr of substantial overdose. (b) AC 50–100 g. (c) Correction of hypotension with supportive measures. Naloxone 0.8–1.2 mg can reverse hypotension. (d) Hyperkalaemia – Glucose 50 g and soluble insulin 15 units.

AMIODARONE

Cl. Fs: Acute overdose causes nausea and vomiting, headache, flushing, paraesthesiae, ataxia, tremor, vertigo, marked bradycardia, hypotension.

Mn.: (a) Gastric lavage. (b) Oral activated charcoal. (c) For severe hypotension dobutamine 5-40 µg/kg/minute. Dopamine 2–5 µg/kg/minute IV should also be given for its effect on renal vasculature.

RESPIRATORY DRUGS

β_2-agonists (Salbutamol, terbutaline, etc.)
Cl. Fs: Palpitations, feeling of excitement, tremor and peripheral vasodilatation. More serious complications include hypokalaemia, ventricular tachyarrhythmias, myocardial ischemia, pulmonary oedema, convulsions, hyperglycemia and lactic acidosis.

Mn: (a) Gastric lavage and activated charcoal. (b) Correction of hypokalaemia. (c) Propranolol 1-5 mg slowly IV will control tachyarrhythmia and also reverse hypokalaemia, but may exacerbate pre-existing obstructive airways disease.

Mn: (a) Supportive care. (b) GI decontamination: GL in patients who presents within 1 hr of sustained-release verapamil or diltiazem. Atropine before lavage. (c) AC followed by repeated doses. Whole-bowel irrigation with polyethylene glycol if sustained release preparation. Generous fluid replacement. (d) Specific treatment: Acidosis should be corrected. Atropine, inotropics, insulin-dextrose and glucagon are probably the best adjunctive treatments.

- Normal saline bolus (10–20 mL/kg)
- 10% calcium chloride 5–10 mL, or 10% calcium gluconate, 10-20 mL every 5 minutes
  - Repeat every 3–5 minutes upto 3 to 5 doses
  - If response, start calcium infusion (10% calcium chloride 1–10 mL/hr)
- Monitor serum calcium after 30 mL of calcium chloride or equivalent
- Glucagon 0.075–0.15 mg/kg i.v. (use water for injection as diluent)
  - Repeat every 5–10 minutes as needed
  - If response, consider infusion of 0.075–1.015 mg/kg/hr
- Atropine, isoprenaline and/or pacing may be tried if symptomatic bradycardia
- Dopamine infusion if persistent hypotension
- If no response to above, start insulin euglycemia therapy
  - Insulin bolus 1 U/kg with glucose, 50% dextrose infusion 0.5 g/hr, adjusted according to hourly glucose checks
- As a last resort, extracorporeal BP support (e.g. cardiopulmonary bypass) may be considered.

THEOPHYLLINE

Cl. Fs.

- Nausea, vomiting, abdominal pain, GI hemorrhage

Mn: (a) AC 50–100 g if given within 1 hr of overdose reduces absorption. MDAC 12.5 g/hr increases elimination. (b) Hypokalaemia – Potassium 40–60 mmol in 1 hr diluted in infusion fluid if severe hypokalaemia. (c) Tachyarrhythmias – Propranolol 1–5 mg by slow i.v. injection (avoided if preexisting obstructive pulmonary disease). (d) Convulsions – 10 mg i.v. diazepam.

10. STIMULANTS AND HALLUCINOGENS

STIMULANTS

Amphetamine

Cl. Fs.: Increased alertness and self-confidence, euphoria, extrovert behaviour, talkativeness, rapid speech, loss of

desire to eat or sleep, tremor, dilated pupils, tachycardia and hypertension. In severe cases excitability, agitation, paranoid delusion, hallucinations with violent behaviour, hypertonia and hyper-reflexia may occur. Convulsions, rhabdomyolysis, hyperthermia and cardiac arrhythmias are uncommon.

Mn.: GL if seen within 1 hr. AC 50–100 g. Diazepam 5–10 mg i.v. or chlorpromazine 50–100 mg i.m. To antagonize peripheral sympathomimetic action of amphetamine propranolol 40–80 mg p.o.

Cannabis

Cl. Fs. of acute intoxication – Euphoria, distorted and heightened images, colours and sounds, altered tactile sensations, sinus tachycardia, hypotension and ataxia. Visual and auditory hallucinations, depersonalization and acute psychosis. Cannabis infusion injected i.v. may cause nausea, vomiting and chills within minutes; after about 1 hr profuse watery diarrhoea, tachycardia, hypotension and arthralgia may develop.

Mn.: Supportive care. Sedation with i.v. diazepam if patient disruptive or distressed. Chlorpromazine 50–100 mg i.m. or haloperidol 2.5–5 mg i.m. may be required.

Cocaine

Cl. Fs.: Acute intoxication produces euphoria, agitation, sinus tachycardia, hypertension, sweating, hallucinations, prolonged convulsions, hyperthermia and rhabdomyolysis. Ventricular arrhythmias, acute myocardial infarction, acute myocarditis, stroke, acute dissection of aorta, renal or intestinal infarction, retinal vascular occlusion and cardiac arrest may complicate severe poisoning.

Mn.: Sedation with i.v. diazepam repeated as necessary to control agitation and convulsions. Active external cooling if temperature exceeds 41°C. Hypertension and sedation usually respond to sedation and cooling. β-blockers are contraindicated because of the risk of precipitating paradoxical hypertension via unopposed a-receptor stimulation. Phentolamine 2–5 mg i.v. or another vasodilator if necessary. Early use of lorazepam with nitrates is more efficacious than nitrates alone in relieving cocaine-associated chest pain.

Hallucinogens (LSD, marijuana, phencyclidine).

LSD

Cl. Fs.: Distorted images, visual hallucinations, agitation and excitement, dilated pupils, sinus tachycardia, hypertension, hyper-reflexia, tremor and hyperthermia are common. Coma, respiratory arrest and coagulation disturbances can occur in those who have snorted large amounts of pure LSD.

Mn.: Reassurance and sedation. If paranoid, chlorpromazine 50–100 mg i.m. or haloperidol 2.5–5 mg i.m., repeated as necessary. Supportive measures. Fluid replacement and maintenance of urine output. Control of convulsions. Phencyclidine induces aggressive behaviour and i.v. diazepam may be required. Haloperidol i.m. may be used if extreme agitation or psychosis.

Ecstasy

Cl. Fs.: Most cases of acute poisoning are characterized by agitation, tachycardia, hypertension, widely dilated pupils, trismus and sweating, hyperthermia, hyponatremia, DIC, rhabdomyolysis, hepatic failure and acute renal failure in severe cases.

Mn.: Diazepam i.v. for agitation. Dantrolene 1 mg/kg i.v. for hyperthermia and dehydration. Hyponatremia responds to fluid restriction. Transplantation if fulminant hepatic failure.

11. CORROSIVES

ACIDS

(a) Inorganic – Hydrochloric, hydrofluoric, nitric, phosphoric and sulphuric acids. (b) Organic – Acetic, formic, lactic and trichloreacetic acids.

Cl. Fs.: Immediate pain in mouth, pharynx and abdomen, intense thirst, vomiting, hematemesis and diarrhoea. Pain and mucosal oedema cause difficulty in swallowing with drooling of saliva. Gastric and oesophageal perforation may occur, with resultant chemical peritonitis (Table 12). Non-GI features include hoarseness, stridor, respiratory distress, and laryngeal and epiglottic oedema. Circulatory shock, metabolic acidosis, acute renal tubular necrosis, renal failure, hypoxemia, respiratory failure, intravascular coagulation and haemolysis may also occur.

Mn.: (a) Acid burns of skin – Irrigation with water or saline for 15–20 minutes. For HCL burns topical application of

Table 12: Grading of corrosive burns of the alimentary tract

Grade	*Feature*
1	Erythema and oedema only
2a	Localized superficial friability, blisters or ulceration
2b	As for grade 2a, but with circumferential ulceration
3	Multiple deep ulcers, areas of necrosis

2.5% calcium gluconate gel and/or s.c. calcium gluconate 0.5 mL 10% for pain relief; it can also be given intra-arterially. (b) Eyes splashed with acid – Irrigation with saline or water. Local anaesthetic for pain. (c) Acid ingestion – clear airway. Endotracheal intubation or tracheostomy may be required for life-threatening pharyngeal or laryngeal oedema. Opioids for analgesia. Soluble calcium tablets 10–20 g for hydrofluoric acid ingestion. Endoscopy should be undertaken as soon as possible. Laparoscopy with resection of necrotic tissue and surgical repair if full thickness necrosis or features of GI perforation.

ALKALIS

Substances encountered include drain, lavatory and pipe cleaners (sodium hydroxide), dishwashing detergents (sodium carbonate and silicate), urinary glucose testing tablets (sodium hydroxide) and alkaline disc batteries.

Cl. Fs.: When ingested, alkalis damage the oesophagus but spare the stomach (except in 20% cases). A burning sensation in mouth and pharynx, epigastric pain, vomiting and diarrhoea. Oesophageal ulceration with or without perforation may occur. Also hoarseness, stridor, respiratory distress, and laryngeal and epiglottic oedema.

Mn.: Endotracheal intubation or tracheotomy for severe pharyngeal or laryngeal oedema. Induced emesis and gastric aspiration and lavage are contraindicated, as also dilution or neutralization of the alkali. Endoscopy should be performed within 12–24 hrs of ingestion. If perforation of GI tract is suspected, or if severe hypopharyngeal burns are present, radiographic studies using water-soluble contrast media should be performed. Corticosteroids may decrease need for surgical repair or strictures e.g. prednisolone 2 mg/kg/day i.v. q8h. until oral intake is resumed, when an equivalent dosage is given p.o. and tapered off over 3–6 weeks.

12. METALLIC POISONING

IRON

Cl. Fs.: Acute iron poisoning can be divided into four phases:

Phase 1 (6–8 hrs): Vomiting and diarrhoea. Vomit and stools are often dark grey or black and in more severe poisoning may become blood stained if ulceration of upper GI tract. Drowsiness, coma, convulsions, shock and metabolic acidosis may develop; shock is out of proportion to amount of GI fluid and blood lost. Progressive circulatory failure and coma may cause death.

Phase 2 (6–12 hrs): Symptoms improve or disappear.

Phase 3 (12–48 hrs): Severe shock, metabolic acidosis and development of jaundice caused by hepatocellular necrosis. Liver failure with hemorrhage, hypoglycemia and renal failure may supervene. Rarely intestinal infarction and infection with Yersinia enterocolitica.

Phase 4 (2–4 weeks): Vomiting caused by gastric stricture or pyloric stenosis.

Mn.: (a) Hospitalization – if ingestion of 20 mg elemental iron/kg body wt. or more. (b) Preventing absorption – GL if seen within 1 hr of ingestion. (c) Whole bowel irrigation if slow-release iron preparation has been ingested and tablets remain in the bowel after GL. (d) Desferrioxamine – if severe poisoning (coma or shock). Dose: 15 mg/kg/hr as i.v. infusion; total dose should not exceed 80 mg/kg in 24 hrs. Alternatively, i.m. doses (2 g b.d. for adult, 1 g b.d. for child).

COPPER SULPHATE

Cl. Fs.: Phase 1: (1–24 hrs) GI symptoms. Phase 2 (24–72 hrs): Hepatorenal damage. Phase 3: Hepatic failure and renal failure. Cause of death is multifactorial – Hypoxemia due to massive haemolysis and methemoglobinaemia affecting brain stem function, toxic myocarditis and renal failure.

Mn.: (a) GL with potassium ferrocyanide (combines with $CuSO_4$ to form cupric ferrocyanide and sulphate, both of which are non-absorbable). (b) Removal of absorbed $CuSO_4$ by chelating agent Penicillamine 2 g p.o. or Dimercaprol 3 mg/kg q8h for 2 days, then q12h for 5 days. (c) Vitamins C and methylene blue to prevent haemolysis. (d) Dialysis for renal failure.

Lead has widespread applications:
Cl. Fs.: Mild intoxication: Lethargy and abdominal discomfort. Severe cases: Abdominal pain (usually diffuse, but may be colicky) vomiting, lethargy, constipation and encephalopathy which is more common in children than in adults. Renal effects include reversible renal tubular dysfunction.

Mn.: Use of chelation therapy is based on symptoms and blood lead concentration. Sodium calcium edetate 75 mg/kg/day is more efficient than DMSA (30 mg/kg/day) in increasing lead excretion, but must be given i.v. Sodium calcium edetate however enhances uptake into the brain, hence oral DMSA is preferred.

MERCURY

Cl. Fs.: Metallic elemental mercury vapour is most important form toxicologically because it is absorbed rapidly

following inhalation. Acute inhalation causes headache, conjunctivitis, cough, nausea and vomiting, metallic taste in the mouth, dyspnoea and chest pain. Chemical pneumonitis and, in severe cases, renal and/or liver failure. Inorganic mercury salts are corrosive and substantial ingestion can cause haemorrhagic gastroenteritis.

Organic mercury salts have been used as fungicides and poisoning usually follows ingestion of contaminated foods.

Mn.: DMPS 30 mg/kg/day p.o. increases mercury elimination and reduces blood mercury concentrations.

ANTIDOTES USED IN HEAVY METAL POISONING

Dimercaprol (BAL) – for arsenic and mercury poisoning. Dose: 2.5–5 mg. kg i.m. q4h for 2 days, then 2.5 mg/kg for 1–2 weeks, as necessary. Side effects – Nausea, vomiting, hypotension, tachycardia, burning sensation in lips, mouth and throat; and feeling of constriction in throat and chest. Water soluble analogues of PAM – DMPS is less toxic and can be given orally in dose of 30 mg/kg. DMSA is used for lead poisoning in a dose of 30 mg/kg.

Sodium calcium edetate – 50–70 mg/kg/day for 5 days i.v. for lead poisoning.

Penicillamine – for copper poisoning. Dose: 0.25–2 g/day until recovery.

Prussian blue – for thallium (used as rodenticide). Dose: 60 mg/kg tid via NGT.

13. POISONINGS FROM INHALED GASES

AMMONIA

Is used in industrial chemicals. At concentrations of > 50 mg/m^3, ammonia vapour is irritant to the eyes and upper respiratory tract, exposure to concentrations > 100 gm/m^3 may lead to severe respiratory distress within minutes and >1500 mg/m^3 are life-threatening.

Ingestion induces severe caustic lesions of the mucous membranes of oropharynx, oesophagus and stomach. Oesophageal or gastric perforation may occur, causing mediastinitis or peritonitis respectively.

Management: (a) Airway: Early intubation should be avoided because an endotracheal tube may increase risk of infection, to which patients are highly susceptible. When intubation is required, the largest practicable tube should be introduced to allow adequate bronchial toilet. Eyes and skin should be irrigated with water immediately and continued for 15–30 minutes. Topical antibiotics may prevent secondary infection of the eye. (b) GI tract – Neutralizing agents should not be administered after ingestion of ammonia water because the resultant exothermic reaction may worsen the injury. Following severe exposure, esophagoscopy is done as soon as possible to introduce nasogastric tube, which is necessary to prevent complete obstruction of the oesophagus. Repeated esophagoscopy about 3 weeks later is indicated in all patients in whom the results of initial esophagoscopy are abnormal.

CHLORINE

Is a greenish-yellow, corrosive gas. At concentrations of >15 mg/m^3, chlorine is irritant to the eyes and upper respiratory tract, exposure above 90–150 mg/m^3 for a protracted period may lead to severe respiratory distress, and above 1200 mg/m^3 are immediately life-threatening with swelling of the larynx and airways with bronchospasm, pulmonary oedema and severe respiratory distress.

Management: There is no specific treatment for airway injury. If intubation is required, the largest tube should be used to allow adequate bronchial toilet.

CARBON MONOXIDE

The two most common sources of gas in acute poisoning are motor vehicle exhaust fumes and smoke from fires. Others include the use of charcoal grills in confined spaces. *Clinical features*: Early—Headache, dizziness, nausea, vomiting and progressive impairment of consciousness. A syndrome suggestive of acute gastro-enteritis has been described. As severity of poisoning increases – hyperventilation, hypotension, increased muscle tone, hyperreflexia, clonus and extensor plantar responses. Skin may be cyanosed. A metabolic acidosis with normal O_2 tension but reduced O_2 saturation is characteristic. Rhabdomyolysis, myocardial infarction, pulmonary oedema, retinal haemorrhages and papilloedema secondary to cerebral oedema are potential complications.

Delayed features of CO poisoning include well-defined neurological conditions:

- Parkinsonism, chorea and choreoathetosis
- Cortical blindness
- Mutism
- Hemiplegia
- Peripheral neuropathy

Characteristics of delayed syndrome include apathy, disorientation, amnesia and hypokinesia in almost all cases. About 50% of patients who show these features start to show them 2–4 weeks after the acute incident.

Management: (a) Patient should be removed from toxic atmosphere. (b) Clear airway, adequate ventilation

and blood pressure should be ensured. O_2 in high concentration. Normobaric O_2 and hyperbaric O_2 improve oxygen delivery to cells by increasing the amount of O_2 dissolved in plasma and reducing the half-life of COHb. Assisted ventilation if necessary. (c) Reduction of increased muscle activity with dantrolene 1 mg/kg i.v. rapidly, repeated as necessary to cumulative maximum of 10 mg/kg. (d) Mannitol and dexamethasone for cerebral oedema. Administration of alkalis is contraindicated because it further impairs O_2 release to tissues through its effect on the oxyhaemoglobin dissociation curve.

SULPHUR DIOXIDE

Cl. Fs.: Exposure to the gas causes lacrimation, rhinorrhoea, cough, increased bronchial secretions, bronchial constriction and, in severe cases, pulmonary oedema and respiratory arrest. Corneal burns can follow eye exposure.

Mn.: Irrigation of eyes and skin with copious amounts of water. Hospitalization in severe cases for treatment of delayed pulmonary oedema. If necessary mechanical ventilation with positive end-expiratory pressure.

NITROGEN

Cl. Fs.: Nausea or minor irritation of upper respiratory tract may occur during first hours post-exposure. After several hours (depending on concentration and duration of exposure), ARDS may manifest.

Mn.: Hospitalization for observation. In severe cases, supportive care and maintenance of gas exchange by mechanical ventilation.

14. MISCELLANEOUS

CYANIDE

Hydrogen cyanide and derivatives (acetonitrile, acrylonitrile, cyanides, nitroprusside and thiocyanate) are widely used in industry.

Cl. Fs.: Acute poisoning—Ingestion by an adult of 50 mL of liquid hydrogen cyanide or 200–300 mg of one of its salts is likely to be fatal without treatment, though death is likely to be delayed for at least 1 hr. In contrast, when hydrogen cyanide gas is inhaled, symptoms occur within seconds, and death within minutes.

Acute poisoning is characterized by anxiety, dizziness, palpitations, headache and weakness. Loss of consciousness, convulsions, cerebral oedema, pulmonary oedema, cardiovascular collapse, cardiac conduction defects, arrhythmias and metabolic acidosis are seen in severe cases.

Tr.: In it addition to O_2, dicobalt edetate 300 mg i.v. if diagnosis is certain. Alternatively, hydroxocobalamin 5 g i.v. over 30 mins. If not available sodium nitrite, 300 mg (10 mL of 3% solution) i.v. over 20 minutes and sodium thiosulphate 12.5 mg (50 mL of 25% solution) i.v. over 10 mins. 4-DMPA is an alternative to sodium nitrite. In severe cases, a second dose of each antidote is required.

QUININE AND CHLOROQUINE

Table 13 gives features of quinine and chloroquine poisoning according to the severity. Quinine is particularly toxic in children, and their management should be a matter of urgency.

Table 13: Features of quinine and chloroquine poisoning

	Severity	*Symptoms*	*Dose ingested (g)*	*Plasma conc. (mg/L)*	*Serum K (mmol/L)*
Chloroquine	Mild	Visual disturbances Vomiting ECG normal	< 2	< 2.5	3.5–4
	Moderate	Vomiting Visual dist. QT increased T wave decreased	2–3.5	2.5–5	2.8–3.5
	Severe	Cardiac failure Convulsions QRS increased	>3.5–4	> 5	< 2.8
Quinine	Mild	Cinchonism	< 10		
	Moderate	Blurred vision QT increased T wave decreased	10–15		
	Severe	Blindness Cardiac failure QRS increased	>15		

Management

Cardiovascular disturbances: Shocked patients—Isoprenaline or adrenaline, which is the drug of choice for severe hypotension in chloroquine poisoning. 8.4% sodium bicarbonate 250 mL for intraventricular block. Cardioversion for VT or VF. Potassium must be administered cautiously in severe hypokalaemia associated with extrasystoles or torsade de pointes.

Diazepam – may have some protective action. Dose: 2 mg/kg within 30 minutes followed by infusion of 2–4 mg/kg/24 hrs.

Gut decontamination: Once patient is stabilized, GL if substantial dose of quinine or chloroquine has been ingested less than 1 hr previously.

Elimination techniques: MDAC if ingestion of life-threatening dose of quinine.

VOLATILE SUBSTANCE ABUSE

Commonly Inhaled Substances

See Table 14.

Clinical Features

Acute intoxication: Initial features like alcoholic intoxication (i.e. initial CNS stimulation followed by depression). Features include euphoria, impaired judgement, feelings of omnipotence, blurring of vision, tinnitus, slurred speech, ataxia, headache, abdominal pain, anorexia, nausea, vomiting, chest pain and bronchospasm. Occasionally, a delirious state is seen with clouding of consciousness and hallucinations. Convulsions, respiratory depression and coma may ensue if inhalation of the volatile substance continues. Arrhythmias (e.g. asystole, severe bradycardia, ventricular fibrillation, due to sensitization of the myocardium to endogenous catecholamines), are a significant cause of death. Inhalation of volatile nitrites may cause the additional problem of severe or even fatal methemoglobinaemia.

Table 14: Commonly inhaled substances

• Toluene containing glue
• Chlorinated hydrocarbons (cleaning fluids, paints, varnishes, lacquers, dyes)
• Fluorocarbons (aerosol propellants, fire extinguishers)
• Petrol
• Acetone (nail polish remover, polystyrene cements)
• Butane
• Propane
• Amyl, butyl and isobutyl nitrites (which may also be ingested)

Chronic abuse: The hair, breath and clothing of chronic abusers may smell of solvent. Bagging (substance sprayed into a plastic bag and inhaled) may cause erythematous spots around the mouth, nose (glue-sniffer's rash). Abdominal pain, nausea, vomiting and hematemesis may be presenting symptoms. Hepatic necrosis is known to occur.

Toluene abuse causes cerebellar damage. Muscular weakness can present as quadriparesis. Petrol and toluene may cause peripheral neuropathy.

Hematuria, pyuria and tubular proteinuria are common in chronic toluene abusers. Renal failure may ensue. Hypochloraemic acidosis may be asymptomatic or present as with severe muscular weakness caused by hypokalaemia or with urolithiasis secondary to hypercalciuria.

Management – is mainly supportive if acute volatile poisoning. Diazepam 10 mg i.v. if necessary to prevent personal harm and injury to others. Methemoglobinaemia can be corrected with methylene blue 1–2 mg/kg body wt. im. if concentrations > 30%. Management of chronic abuse is psychological.

Lithium

Cl. Fs.: Neurological, GI, cardiovascular and renal disturbances occur.

ST-T changes on ECG, and more rarely conduction disturbances may also occur.

Grades of severity:

- Grade 1 : Drowsiness, nausea, vomiting, tremor, hyperreflexia, agitation, muscle weakness, ataxia
- Grade 2 : Stupor, rigidity, hypertonia, hypertension
- Grade 3 : Coma, convulsions, myoclonus, collapse

Therapeutic serum lithium concentrations are normally 0.8–1.2 mmol/L, moderate toxicity is seen at 2.5–3.5 mmol/L, and severe symptoms are seen at more than 3.5 mmol/L. However in acute poisoning, symptoms may be absent or minor despite high serum concentrations. In acute-on-chronic poisoning, severe symptoms occur more rapidly.

Mn.: GL if ingestion of more than 40 mg of lithium carbonate/kg body wt less than 1 hr previously. Isotonic sodium chloride 2–3 liters/day in absence of renal failure or CCF. Haemodialysis is treatment of choice for rapid removal of lithium from the body. A rebound increase in lithium serum concentrations may be observed because of the

slow diffusion of lithium from the intracellular to extra cellular compartment.

THYROXINE AND TRIIODOTHYRONINE

Only a small percentage of patients who ingest even a substantial single overdose of thyroxine (T4) or triiodothyronine (T3) develop features of toxicity.

Cl. Fs.: Symptoms may develop within a few hours of T3 ingestion but are not usually maximal for 3–6 days after T4 ingestion. Features tend to resolve in about the same time as they take to develop. Palpitations, tremor, anxiety, irritability, hyperactivity, fever, tachycardia and insomnia are most common. Atrial fibrillation, sweating and loose stools are rare.

Mn.: AC in patients who present within 1 hour of substantial overdose. Serum T4 and T3 concentrations should be measured in blood taken 6–12 hours after ingestion; a normal result excludes possibility of delayed toxicity. Patients in whom the hormone concentrations are high should be observed for evidence of toxicity; if this develops, they should be given propranolol 40 mg t.d.s. 5 for days.

WARFARIN AND OTHER ANTICOAGULANTS

Warfarin toxicity is more likely to occur in the setting of therapeutic anticoagulation than as a consequence of acute ingestion.

Cl. Fs.: Epistaxis, gingival bleeding, spontaneous bruising, hematomas, bilateral flank pain, rectal bleeding and hemorrhage into any organ may occur. Severe blood loss may result in hypovolemic shock, coma and death.

Management

Intention to continue anticoagulant

- INR <6 but >5 above target value: Reduce dose of warfarin or restart when INR <5
- INR 6-8 and patient not bleeding, stop warfarin and restart when INR <5
- INR >8, and patient not bleeding, stop warfarin and restart when INR <5

If other risk factors for bleeding, give vitamin K_1 0.5 mg i.v. slowly. Unnecessarily large doses of vitamin K should be avoided because it can result in loss of patency of vascular graft. If major bleeding occurs, give vitamin K_1 5 mg by slow i.v. injection, with prothrombin complex concentrate 50 U/kg, or, if not available, fresh frozen plasma 15 mL/kg.

Camphor is a pleasant smelling cyclic ketone with propensity to cause neurologic side effects especially seizures. Vast majority or camphor toxicity are due to accidental oral ingestion especially in the paediatric age group, few case reports suggest absorption through nasal inhalation, nasal instillation and through the skin (practice of "Cao Gion or coining") as well as suicidal intake. With significant ingestion of camphor 50 mg/kg body wt, neurologic toxicity is common, with generalized tonic clonic activity occurring from 5 to 90 minutes after exposure.

Tr.: Since camphor is rapidly absorbed after ingestion from GI tract, neither activated charcoal nor gastric lavage is helpful. Benzodiazepines should be used to control seizures. Because of camphor's highly lipophilic nature, extracorporeal procedures to remove the toxin from the body are questionable.

Aluminium phosphide is primarily used by agriculturists, as a fumigant to destroy insects and rodents and is also used for suicide. Following ingestion, there is a metallic taste in the mouth followed by nausea, frequent vomiting with retching, diarrhoea and abdominal pain. There may be garlicky taste and smell. The liberated phosphine gas causes dyspnoea, pulmonary oedema and bradycardia followed by circulatory collapse.

Tr.: No specific antidote. If skin and clothes are soiled with vomitus they should be removed. Gastric lavage with 3-5% solution of sodabicarb which minimises conversion to phosphine. Milk and strong tea should be freely given. Penicillamine 20 mg/kg body wt is useful. Other supportive measures include glucose saline, vitamin K and corticosteroids and pentazocine for pain.

Hair dye: Most hair dyes contain paraphenylenediamine (DPD). Hair dye ingestion causes angioedema of face and neck, dysphagia, chocolate brown coloured urine, bodyache and tender muscles. *Tr.* – No antidote. Diphenhydramine and steroids. Tracheostomy for severe angioedema. Acute renal failure requiring dialysis can be a delayed complication.

15. VENOMOUS BITES AND STINGS

SNAKE BITE

Common poisonous snakes: (a) Elapids – Indian cobra, common krait. (b) Vipers – Russell's viper and saw-scaled viper.

Venoms: Components of the venom usually reach the circulation via the lymphatics, though low molecular weight components may be absorbed directly into the capillaries. Most venoms are complex mixtures of many different toxins. (a) *Proteinases* act as cytotoxins, causing local swelling and damage in the region of bite. (b) *Neurotoxins* interfere with neuromuscular transmission; some phospholipase A2 toxins also damage myocytes directly. (c) Some venoms contain *haemorrhagins* which cause bleeding. (d) Coagulopathies may be caused by action of venom components at different sites in the coagulation pathway leading to a state resembling DIC. Venom components also act directly on platelets.

Clinical features: Depend on the species. The bite of elapid snakes (kraits, cobra) most commonly causes neurotoxicity, whereas viperine snakes (vipers, rattle snakes) cause local tissue damage, shock and coagulopathies.

Systemic Effects

- Symptoms of systemic envenoming (headache, lymph node pain and collapse) can occur within several minutes of the bite. Most signs of envenoming develop within a few hours, though neurotoxicity can occasionally take more than 12 hours.
- Fang marks are usually visible at site of the bite.
- Following bites from some species, oedema can occur at the site of the bite and progress to the whole limb. Some species cause tissue necrosis at the site of the bite.
- Painful regional lymph nodes enlargement is a common early sign.
- Venom haemorrhaging act on endothelium, causing bleeding form the gums and other sites (e.g. oral sores).
- Coagulopathies can exacerbate this effect, and occasionally lead to life-threatening bleeding.
- Shock can occur as a result of loss of fluid into a limb or haemorrhage.
- Neurological involvement classically causes progressive paralysis. Ptosis occurs initially; this progresses to involvement of bulbar muscles and ultimately, paralysis of the diaphragm.
- Destruction of skeletal muscle, following envenoming by species, such as sea snakes, leads to painful myopathy and paralysis.
- Renal failure complicates envenoming by several species.

Investigations: WBC count is commonly elevated and thrombocytopenia often occurs; particularly in patients with coagulopathy. Renal function should be checked. Creatine kinase elevation occurs in myotoxicity.

Whole blood clotting test is an important bedside indicator of envenoming by species that cause coagulopathy. Blood left in a clean glass tube is examined after 20 minutes to see whether clotting has occurred. In some cases the test can also be used to follow the response to antivenom. Standard clotting assays (PT, APTT, fibrinogen) are sensitive indicators of a coagulopathy.

Management

1. *Local treatment*: (a) *Measures to prevent absorption of poison* – If patient is seen shortly after the bite, application of pressure bandage 2 inches proximal to site of bite. Arterial tourniquets are painful and even dangerous short-term method of delaying systemic spread of venom. Firm pressure with a pressure bandage over the site of venom injection, combined with immobilization of the limb involved results in marked retardation of venom movement. Most traditional first aid procedures (e.g. incision, suction) are more harmful than beneficial. Antivenom is indicated for systemic or severe local reactions. (b) If patient is seen late the swelling and inflammation should be treated by elevation of the limb, mag. sulph. compresses, heparinoid ointment and broad spectrum antibiotic. (c) *Surgical debridement and skin grafting* – may be necessary at a later stage in case of extensive necrosis.
2. *Antivenom*: Anti-snake venom serum available as freeze dried powder for easy storage. It is reconstituted by adding distilled water. Sensitivity should be tested by giving in intra-dermal test dose, 20 mL (though according to some test dose has no role in predicting antivenom reactions) of the serum is given IV as first dose slowly over 20 minutes. Second dose can be repeated 2 hours later if symptoms persist. Further doses can be repeated 6-hourly till symptoms disappear. Children require same dose as adults.
3. *General management*: (i) Tetanus toxoid 1 mL i.m. (ii) Antihistamines to reduce severity of allergic and inflammatory reactions. (iii) Analgesics for local pain. (iv) Sedation with diazepam. (v) Corticosteroids – IV hydrocortisone 100 mg. 6 hourly in case of severe shock, generalised allergic reactions and sensitivity reactions due to serum. (vi) An Edrophonium chloride test may be done in patients with neurotoxicity. If patient responds, he should be maintained on neostigmine.

   There is no role for routine prophylaxis but adrenaline should always be available for treatment of reactions.

Effective treatment should halt local oedema and reverse coagulopathy in within 6–12 hours. The whole blood clotting test 6 hours after administration, or measurements of PT or APTT after 6 hours can help determine if further doses are necessary.

Most toxins acting postsynaptically are reversed by antivenom, but presynaptic neuropathy is less responsive, supportive therapy may be needed until spontaneous recovery occurs.

Delayed absorption of venom from a depot at the site can occur. Repeated doses of antivenom may be needed if coagulopathy redevelops, neurological deterioration occurs or limb oedema progresses.

4. *Management of complications* – (a) Care of the airway is critical in severe neurotoxicity. Bulbar involvement (demonstrated by inability to swallow secretions) is an indication for early intubation and mechanical or non-invasive ventilation if facilities are available. (b) Hypotension requires appropriate management with fluids. (c) For kidney failure peritoneal dialysis can be life-saving. (d) Fasciotomy is seldom required, even in severe oedema. The only indication is raised intracompartmental pressure. Surgery should not be performed until coagulopathy has been corrected.

BEE AND WASP STINGS

CL. FS.: People who have become sensitized to bee venom usually suffer increasingly severe reactions to successive stings. There is excessive local swelling and in severe cases, generalised urticaria, or bronchospasm with or without laryngeal oedema. Anaphylactic reaction may occur.

TR.: (a) The sting with its attached venom gland must be removed by scraping off with the blade of a knife. (b) Antihistamines for mild reaction, adrenaline for severe reaction. (c) Steroids – Single dose of 20-30 mg prednisolone may suffice.

SCORPION STING

Scorpions sting through the telson at the tip of their tails. The Indian red scorpion is small in size with segmented tail and is very poisonous. The black scorpion is less poisonous.

Clinical manifestations: Depend upon the species of scorpion and dose of venom injected at time of sting.

1. *Local*: Excruciating pain at sting site, sudden tap at or around the site of sting induces severe pain (Tap sign).
2. *Systemic*: (a) Transient projectile vomiting. (b) Profuse sweating (skin diarrhoea). (c) Thick ropy salivation. (d) Priapism. (e) Cold extremities. (f) Mydriasis. (g) CVS-hypertension, cardiac arrhythmias, tachybradycardia, pulmonary oedema, hypotension and shock are but one process of ongoing "autonomic storm". (h) Neurological: Hemiparesis haemorrhagic or thrombotic stroke due to DIC. (i) Acute pancreatitis.

TR.: (a) Local infiltration with 1% lignocaine, cold therapy at the site, analgesics. (b) Scorpion antivenom (SAV) – Without skin test SAV must be administered as soon as possible by IV route. Nonspecies F(ab) SAV is available. The maximum volume of venom injected in one sting by Indian red scorpion is 1.5 mg and each ml of antivenom is capable of neutralizing 1.2 to 1.5 mg. venom, hence 30 ml of antivenom should suffice, however more may be required for severe sting. (c) Prazosin – 250–500 mcg orally q3h is a physiological and pharmacological antidote to scorpion venom actions. (d) Dobutamine infusion 5–20 mcg/kg/min given in hypokinetic phase (hypotension, shock, tachycardia, delirium) with or without pulmonary oedema causes improvement in clinical condition. (e) Nitroglycerine (NTG) drip 0.5 to 5 mcg/kg/min in addition to dobutamine improves myocardial dysfunction and reduces pulmonary congestion. (f) Pulmonary oedema cases improve with dobutamine, mechanical or non-invasive ventilation or by helmet-derived non-invasive pressure support ventilation.

SPIDER BITES

Venom is injected through the fangs.

Clinical Syndromes

1. *Necrotic araneism*: Local burning, transient fever and erythematous rash, intravascular haemolysis and development of ischemic local lesion which forms a necrotic black eschar. Tr. – (a) Antivenom. (b) Dapsone may reduce extent of necrosis. (c) Skin grafting after eschar has sloughed.
2. *Neurotoxic araneism*: Bite is very painful. Systemic symptoms include headache, vomiting, muscle spasms, priapism, pulmonary oedema and coma. Tr. – (a) Arterial tourniquet or splinting with crepe bandage to prevent absorption of neurotoxins. (b) Specific antivenom. (c) Calcium gluconate for muscle spasms.

VENOMOUS JELLYFISH STINGS

Cl. Fs.: Immediate pain at site of contact is followed by acute inflammatory response, which can be sufficiently severe to cause full-thickness skin damage. Severe myalgia and panic, hypertensive crisis, acute pulmonary oedema and autonomic disturbances.

Mn.: Local use of ice, vinegar and compressive bandaging (effective on stings from box jellyfish). Stings from hydroids (e.g. Portuguese man-of-war) washed with sea

water and adherent tentacles picked off. Antivenom if available. First aid and resuscitation if large amounts of venom are absorbed.

MULTI BEE STINGS

Acute myocardial injury and rhabdomyolysis caused by multiple bee stings result of direct toxic effect in venomation and secondary to systemic anaphylactic reaction. It can also cause haemolysis with acute kidney failure.

16. CHEMICAL AND BIOLOGICAL WARFARE AND TERRORISM

The acquisition of chemical and biological weapons has increased the incidence of their use. Clinicians and other specialists must be prepared to treat civilians exposure to chemical weapons.

See Table 15 for summary of the agents.

Yellow phosphorus poisoning (smoking stool syndrome)
Diagnosis can be suspected if there is evidence of cutaneous burns, garlic odour in vomitus or faeces, 'smoking' and luminescence of vomitus and faeces, and characteristic course with asymptomatic middle phase. If more than 1 g is consumed, patient dies of cardiovascular collapse or acute yellow atrophy of liver. Tr. – No specific antidote. Gastric lavage with Pot. permanganate 1:5000, or 0.2% copper sulphate solution. Supportive measures.

Jatropha cureas poisoning

The plant is used as a laxative, parasitic and vermifuge. It is also used as biofuel. Symptoms -Vomiting followed by abdominal pain and loose stools. Ingestion of one or two seeds causes toxic symptoms of short duration. High concentration of phorbol esters present in the seed is the main toxic agent. Tr. is symptomatic with rehydration, salts and IV fluids.
Isopropanol poisoning. Isopropanol is found in after-shave lotions, disinfectants, and is used as sterilizing agent.
Cl. Fs.: Cardiac and respiratory depression are common, but hematemesis, hypotension, hypothermia, renal tubular acidosis can occur.
Mn.: In severe cases, haemodialysis.

Table 15: Chemical and biological warfare agents

Agent	*Mechanism of toxicity*	*Features of toxicity*	*Management*
A. Chemical agent • *Nerve agents* Sarin (GB) Tabun (GB) Soman (CD) (Dermal and resp. hazards) VX (contact poisons)	Inactivate acetylcholine esterase (Ach) enzyme resulting in muscarinic, nicotinic and CNS effects	*Mild/Moderate* Miosis Blurred vision, Headache, Sweating, vomiting, *diarrhoea*, muscle fasciculation, *severe* All above Convulsions, Coma	Decontamination Sedation Oxygen Atropine 2 mg IV over 5 mins. till effective or IM if not possible, Pralidoxime 600–800 mg IM or 1–2 g IV over 20–30 min. Lorazepam or Diazepam for seizures
• Asphyxiants - Blood asphyxiant Hydrogen sulphide Hydrogen cyanide - Choking agents Chlorine Phosgene Sulphur dioxide Nitrogen dioxide	Bind with iron in cytochrome preventing cerebellar O_2 consumption React with cytoplasmic proteins to destroy cell structure	*Mild/moderate* Palpitations, dizziness, headache, hyperventilation, drowsiness, hypotension *Severe* Convulsions, Coma, Fatal within 5 mins. Breathlessness Wheezing Laryngeal spasm Pulmonary oedema Dermal irritation ARDS	O_2 (100%) by facial mask or intubation. Amyl nitrate inhalation 1 am q5 min Sodium nitrate 200 mg IV Sodium thiosulphate 12.5 g IV
• Vesicants Mustard gas Lewisite Phosgene oxime	Mustard forms metabolites that bind to enzymes and proteins Binds to thiol group in number of enzymes Corrosive action like strong acids	Burning and itching of skin Burning eyes, lacrimation Dyspnoea Redness of skin and blistering Nausea, vomiting Skin erythema, blistering, swollen eyes, lacrimation, pulmonary oedema	Mn. of secretions O_2 Tr. of pulmonary oedema with PEEP to maintain $PO_2 > 60$ mm Hg No specific antidote, supportive care Burn therapy For lewiste BPL IM

CHAPTER

15

Dermatology

1. STRUCTURE AND FUNCTIONS OF NORMAL SKIN

Normal epidermis is a terminally differentiated, stratified squamous epithelium comprising predominantly keratinocytes. Many skin diseases affect keratinocytes. Common hallmarks of epidermal involvement are:

- Abnormal scaling of skin
- Vesicle formation
- Erosion caused by complete loss of the epithelial layer

Stratum corneum comprises anucleate, keratin-filled squames; it forms a barrier on the surface of the skin, protecting the living layer from damage by desiccation and mechanical trauma. The integrity of this barrier is dependent on the keratin cytoskeleton and the adhesion molecules that hold the keratinocytes together and maintain their attachment to the basement membrane.

Basal layer. Epidermal stem cells in the basal layer divide to form transient amplifying cells which then migrate suprabasally, cease dividing and undergo terminal differentiation.

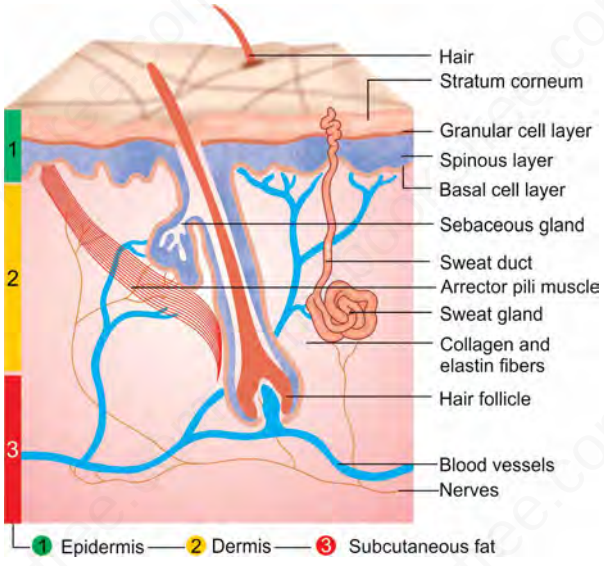


Fig. 1: Normal skin structure

Melanocytes are found in the basal layer of epidermis, which forms on structures termed 'melanosomes' which are passed on to keratinocytes and form a protective 'cap' over the nulcei of these cells.

Langerhans cells in the epidermis process antigen and activate naive T cells in lymph nodes that then acquire the capacity to circulate preferentially to the skin.

Dermis is a complex tissue comprising many different cell types. Changes in the dermis such as vasodilatation and accumulation of inflammatory cells often accompany disease, such as psoriasis, eczema and lichen planus. Absence of signs of epidermal involvement and awareness of the cellular composition and pathology of the dermis assists in diagnosis.

Regional variations in skin anatomy and disease localization.

The composition of human skin varies between body sites as a result of difference in the thickness of the interfollicular epidermis, and in the size and number of skin appendages, including hair follicles, sebaceous glands and apocrine glands. These regional differences have a key role in determining the localization and effects of different disease processes on the skin.

In addition to these morphological variations, there is evidence of marked differences in the expression of various proteins at different body sites. These are best illustrated in patients with palmoplantar keratodermas in which disease is restricted to the normal sites of expression of the mutant protein.

Hair follicles: Normal hair follicles when fully developed enter a hair cycle characterized by a growing phase (anagen), a resting phase (telogen) and a regressing phase (catagen). Illness can induce premature entry of anagenic hair follicles into telogen, and this causes increased hair shedding and temporary thinning of the hair (telogen effluvium).

Skin immune system: The skin has an important role in host defence. When the skin is exposed to a new antigen, activated antigen-expressing Langerhans' cells migrate from the skin to the lymph nodes, where they activate naive T cells, which become memory T cells, and express new surface markers that allow them to accumulate in the skin in response to cutaneous injury.

2. DERMATOLOGICAL HISTORY AND EXAMINATION

HISTORY

Symptoms: Intense itch in some eruptions (e.g. scabies, atopic dermatitis, lichen planus). In pityriasis versicolor there is often mild itching after a hot bath. Other types of symptoms include pain (e.g. chondrodermatitis of the ear, burning, chilblains and tenderness (e.g. erythema nodosum). Urticaria affecting palms often causes pain (because the edema is deeper and the firmer tissues of the palm cannot distend easily).

Duration, evolution, periodicity. In urticaria, individual lesions change from day to day, in erythema multiforme, lesions are relatively static. Overall duration is of help in localized lesions, e.g. in presumed keratoacanthoma still enlarging after a few months is probably a squamous cell carcinoma.

Some dermatoses have a characteristic evolutionary sequence (e.g. pityriasis rosea, in which a solitary larger 'herald patch' precedes the widespread eruption by a few days).

Medical history and medications: Situations in which systemic disease should be considered include unusual patterns of ulceration, e.g. pyoderma gangrenosum related to ulcerative colitis, acquired ichthyosis or generalized pruritus without rash in younger patients.

Medications may cause skin eruptions. Previous topical therapy may obscure clinical features (e.g. topical corticosteroids applied to ringworm infection, causing 'tinea incognito'). History of sun exposure and unprotected sex.

Family history may be important in genodermatoses (e.g. neurofibromatosis), and in some disorders with more complex inheritance (e.g. atopic dermatitis, psoriasis).

Occupation and hobbies: Hands are the most commonly affected site in occupational dermatitis. Hobbies can cause problems, e.g. epoxy resins adhesives, rubber chemicals (footwear, gloves) and plants are common allergens.

PHYSICAL SIGNS

See Table 1 for the shape and pattern of skin lesions.

Arrangement and symmetry. Asymmetrical eruptions often have external cause, e.g. unilateral palmar involvement in fungal infection. Also in cooks, hairdressers and others who hold a tool in the dominant hand while handling irritant materials with the other.

Distribution. Some disorders have a predilection for specific body sites.

Scalp: Hair disorders, alopecia, psoriasis, seborrhoeic dermatitis, lichen simplex (nape of neck), pilar cysts, organoid naevus (hamartoma), cutaneous metastases of internal malignancy.

Eyelids: Atopic dermatitis, contact allergy (cosmetics, nickel), seborrhoeic blepharitis, angio-oedema, dermatomyositis, basal cell carcinoma, xanthelasma.

Face: Acne, atopic dermatitis, seborrhoeic dermatitis (particularly eyebrows and nasolabial crease), butterfly rash (rosacea, erysipelas, lupus erythematosus, lupus pernio, erythema infectiosum), naevi and freckles, actinic

Table 1: Shape and pattern of skin lesion

Shape	*Description*	*Examples*
Discoid	Filled circle	Discoid eczema
Petaloid	Discoid lesions that have merged together	Seborrhoeic dermatitis on the trunk
Arcuate	Incomplete circles	Urticaria
Annular	Open circles, central skin different from that of the rim	Tinea corporis, granuloma annulare (Fig. 2)
Polycyclic	Circles that have merged together	Psoriasis
Livedo	'Chicken wire' criss-cross pattern	Erythema ab igne, vasculitis
Reticulate	Fine, lace-like pattern	Oral lichen planus
Target	Multiple concentric rings	Erythema multiforme
Stellate	Star-shaped	Lesions of meningococcal septicaemia
Digitate	Finger-shaped	Chronic superficial dermatosis
Linear	Straight line	Koebner reaction to a scratch, lichen planus
Serpiginous	Snake-like	Cutaneous larva migrans

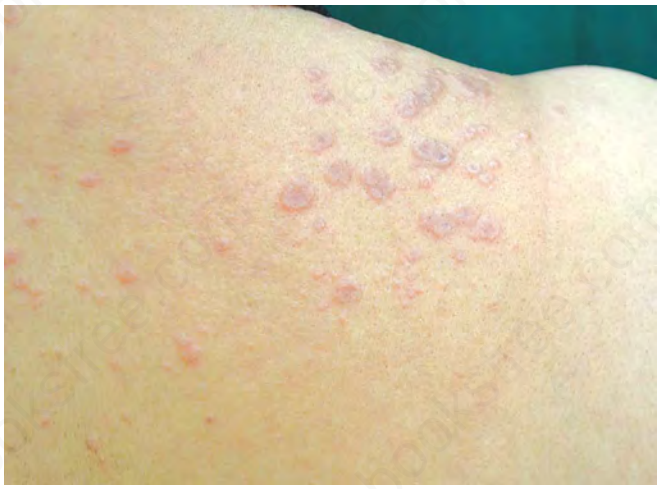


Fig. 2: Granuloma annulare

keratoses, basal and squamous cell carcinomas, keratoacanthoma, lentigo maligna.

Lips: Dermatitis (atopic, contact), cheilitis (angular, actinic), angio-oedema, contact urticaria, impetigo, erythema multiforme, warts, vascular lesions (venous lake, pyogenic granuloma), squamous cell carcinoma.

Hands: Dermatitis (dyshidrotic, pompholyx, contact), psoriasis and palmoplantar pustulosis, keratodermas, dermatophyte infections, erythema multiforme, photosensitivity (dorsal hand), scabies (particularly finger webs), collagen vascular disorders and vasculitis (particularly nail-fold and fingertip), viral warts, actinic keratoses, squamous cell carcinoma, granuloma annulare, nail disorders.

Limbs: Psoriasis, atopic dermatitis (limb flexures), discoid eczema, venous eczema and ulceration (lower leg), asteatotic eczema (lower leg), lichen simplex (lower leg), lichen planus (flexor forearms, shins), dermatitis herpetiformis (knee, elbow), erythema nodosum (legs), vasculitis (legs), papular urticaria, flea bites (lower leg), dermatofibroma, Bowen's disease (lower leg).

Feet: Dermatitis (pompholyx, contact, juvenile plantar), psoriasis and palmoplantar pustulosis, dermatophyte fungal infection (skin and nails), pitted keratolysis, vasculitis and arterial disease, callosities, corns, verrucae.

Axillae: Psoriasis, contact dermatitis, staphylococcal boils, hidradenitis suppurativa, acanthosis nigricans, erythrasma, fibroepithelial polyps, freckles in neurofibromatosis (Crowe's sign).

Genitals: Scabies, Psoriasis, Reiter's syndrome, lichen planus (penis), lichen sclerosus (penis, vulva), lichen simplex (scrotum, vulva), fixed drug eruption (penis), sexually transmitted diseases/genital warts, Zoon's balanitis (glans penis), epidermoid cysts (scrotum), squamous cell carcinoma (penis, vulva). Fixed drug eruption.

Table 2: Morphology of skin lesion

• Macules (flat patches)
• Plaques (flat-topped but palpable)
• Papules and nodules (dome-shaped, flat-topped, umbilicated or crusted)
• Blisters (vesicles, bullae)
• Pustules
• Various breaks in skin (ulcers, erosions, fissures)

Colour: (a) Shades of red, e.g. violaceous colour of dermatomyositis or lichen planus, brownish-red of seborrhoeic dermatitis, and pillar-box red of erysipelas. (b) Non-blanching on pressure in extravasation of blood. Scaling alters colour by introducing hair-keratin interspaces. (c) Inflammation of the skin disrupts pigmentation. Residual pigmentation is a characteristic feature of lichen planus.

Close-up morphology: Accurate description of skin lesions is based on recognition of morphology as given in Table 2.

Changes in the skin in form of thickening and thinning can be made out by both palpable and visible physical signs (e.g. increased skin markings in lichenification, more visible vessels as a result of atrophy). Scaling and crusting imply an epidermal contribution; thus annular lesions of ringworm (scaly) and granuloma annulare (no scaling). Also quality of scale (e.g. large, hard, silvery scale of psoriasis, fine 'bran-like' scales of pityriasis versicolor).

Interventional physical signs: (a) Feeling of skin in assessing thickness of lesions, texture, tethering and temperature. (b) Application of oil to the skin fills air spaces (e.g. identification of Wickham's striae in lichen planus). (c) Diascopy compresses vessels and reduces erythema allowing other colours to be seen (e.g. brownish translucency in sarcoid). (d) A scalpel can be used to exaggerate the minor scaling of pityriasis versicolor, and to obtain scale samples of fungal cultures. (e) A needle can be used to extract scabies mites from the skin. (f) Wood's light is used to distinguish epidermal from dermal pigmentary abnormalities, and for fluorescence of scales in tinea capitis (but only caused by cat or dog ringworm) and some other infections and dull green in favus.

Combination of physical signs, e.g.

- Discrete scaling plaques: Examine nails for psoriatic pit, onycholysis
- Scattered, discrete purplish lesions: Examine mouth for striae of lichen planus

- Erythema and scaling of one palm or 'asymmetrical eczema': Examine feet to confirm tinea pedis.

3. DERMATOLOGICAL PHARMACOLOGY

TOPICAL THERAPY

The effectiveness depends on their ability to penetrate the epidermis and is influenced by the choice and concentration of the drug, its vehicle or base, and the age and degree of hydration of the skin. The site to be treated is also important, e.g. absorption is greater at flexural sites and face.

Vehicles hydrate the skin, can have anti-inflammatory effect, and help the active drug penetrate the skin.

Creams are water-based products with a cooling and emollient effect. They contain preservatives to prevent bacterial and fungal growth. Creams are less greasy than ointments and are cosmetically better tolerated.

Ointments are oil-based products which provide an occlusive layer over the skin surface that helps enhance absorption, and are therefore useful in chronic dry conditions.

Lotions are watery suspensions which can be used over hairy and large body surface areas. They have a drying, cooling effect.

Gels are watery suspensions of insoluble drugs such as corticosteroids, salicylic acid and retinoids. Gelling agents are added to aid their absorption.

TOPICAL AGENTS

Indications for various topical agents is given in Table 3.

Emollients: The term 'emollient' covers a diverse range of products including soap substitutes, bath additives, creams, ointments and even an aerosol spray product. They are important in management of itchy, dry skin conditions, giving symptomatic relief. Their effects are temporary, and frequent applications are needed. Emollient creams, ointments and sprays are best applied following a bath.

Topical corticosteroids: Cutaneous effects include vasoconstriction, reduced dermal blood vessel permeability and inhibition of phospholipases, fibrin and kinins. Table 4 gives topical corticosteroids classification according to their potency.

In addition, inhibition of phospholipases leads to blockage of the arachidonic acid pathway, which leads to a cascade of inflammatory mediators; anti-inflammatory effects thus occur.

Inflammatory skin conditions involving the delicate skin on the face or genitalia require a mild or moderately potent corticosteroid, in contrast, palms, soles and markedly thickened skin (as may occur in chronic scratching) often require a potent or very potent agents.

The *quantity* applied can be assessed using the 'fingertip unit' concept – An amount of ointment or cream, the length of an adult fingertip is about 0.5 g and is sufficient for 300 cm^2 of affected skin (thus, a single application for one arm or leg requires 3FTU or 6FTU respectively).

Tropical retinoids act via nuclear retinoid receptors.

Tazarotene is a selective retinoid receptor agonist with anti-inflammatory and antiproliferative effects on keratinocytes. It is used for plaque psoriasis affecting up to 10% skin area. It should be avoided in women of childbearing age, and on facial and sexual skin.

Adapalene is used for acne, both comedonal (Fig. 3) and inflammatory.

Tretinoin and isotretinoin are useful in comedonal acne but have little effect in inflammatory acne.

Tazarotene is a potent selective retinoid. It should be avoided in seborrheic dermatitis and in pregnancy.

Topical vitamin D derivatives are first-choice topical therapies in treatment of psoriasis, and can be combined with topical corticosteroids and phototherapy.

Calcipotriol is used in treatment of mild to moderate plaque psoriasis affecting up to 40% body surface area. It is contraindicated in pregnancy and should not be used on the face.

Table 3: Indications for various topical agents

Topical agents	*Indications*	*Side effects*
Corticosteroids	Inflammatory Dermatoses	Striae, telangiectasiae, bruising, contact dermatitis,
Emollients	Xerosis, eczema, psoriasis	depigmentation, worsening of infection, rebound phenomenon,
Retinoids	Psoriasis, acne, photo-damage	suppression of hypothalamic-pituitary-adrenal axis
Vitamin D analogues	Plaque psoriasis	Folliculitis
Coal tar	Plaque psoriasis	Skin irritation, erythema
Dithranol	Plaque psoriasis	Skin irritation, pruritus, erythema, hypercalcaemia
		Skin irritation, staining folliculitis, skin cancers
		Skin irritation, staining

Table 4: Topical corticosteroids classified according to their potency

Potency	*Corticosteroid*	*Risk of skin thinning with long-term use*
Mild	Hydrocortisone	Low
Moderate	Clobetasone butyrate	Some risk
Potent	Betamethasone valerate	High
potent	Hydrocortisone butyrate	Very high
Very	Clobetasol propionate	

Table 5: Systemic agents

Agents	*Indications*	*Dose*	*Monitoring*	*Side effects*
Acitretin	Psoriasis, Ichthyosis	0.2–1 mg/kg o.d.	FBC, LFTs, lipids, spinal radiography	Mucosal dryness, epistaxis, myalgia, alopecia, teratogenicity, hyperlipidemia, mood changes, diffuse interstitial skeletal hyperostosis
Isotretinoin	Acne	0.5–1 mg/kg o.d	FBC, LFTs, lipids	As above
Cyclosporine	Eczema Psoriasis	2.5–5 mg/kg o.d.	FBC, LFTs, urea and electrolytes, BP, creatinine clearance	Renal impairment, infections, hypertension, gum hypertrophy, Hirsutism
Azathioprine	Autoimmune and bullous disorders	1–3 mg/kg o.d.	FBC, LFTs, urea and electrolytes	GI symptoms, infections, myelosuppression, hepatotoxicity
Methotrexate	Psoriasis	5–25 mg/week	FBC, liver biopsy, urea and electrolytes, LFTs	GI symptoms, stomatitis, myelosuppression, liver fibrosis, nephrotoxicity

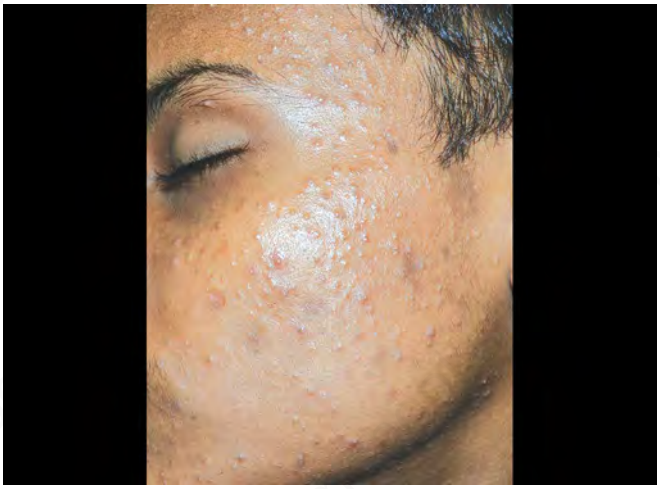


Fig. 3: Comedonal acne

Table 6: Classification of alopecia

A. *Non-scarring:*
1. Patchy:
– Alopecia areata
– Tinea capitis
– Androgenic alopecia
– Traction alopecia
2. Diffuse:
– Alopecia universalis
– Ectodermal dysplasia
B. *Scarring:*
• Congenital-Alopecia cutis
• Infective-Favus, kerion
• Inflammatory: Lichen planopilaris, discoid lupus erythematosus
• Neoplastic: Basal cell carcinoma
• Nevi: Nevus sebaceous
• Injury: Physical, chemical
• Idiopathic

SYSTEMIC THERAPIES

Indications, dosage, monitoring and side effects of systemic agents are listed in Table 5.

4. HAIR AND NAILS

HAIR DISORDERS

Alopecia can be divided into cicatricial and non-cicatricial. Non-cicatricial alopecia can be divided into patchy and diffuse alopecia. Cicatricial alopecias have poor prognosis. Table 6 gives the classification of alopecia.

Patchy Alopecia

1. ***Alopecia areata:*** A non-scarring autoimmune disorder affecting any hair-bearing area. Typically, there is a sudden onset of well circumscribed, totally bald, smooth patch, often with 'exclamation-mark' hairs at the border, usually affecting the scalp (Fig. 4). Spontaneous growth frequently occurs, but the areas may spread peripherally and may eventually involve the whole scalp (alopecia totalis). The reason why white hairs appear to be relatively spared compared with pigmented hair is not understood (this phenomenon may explain reports of sudden greying and hair turning white overnight). Alopecia areata in atopic individuals has a worse outcome.

   Aetiology: (a) *Genetic predisposition* – Family history increases likelihood. (b) *Association with autoimmune diseases* (thyroid disease, vitiligo and Addison's disease)

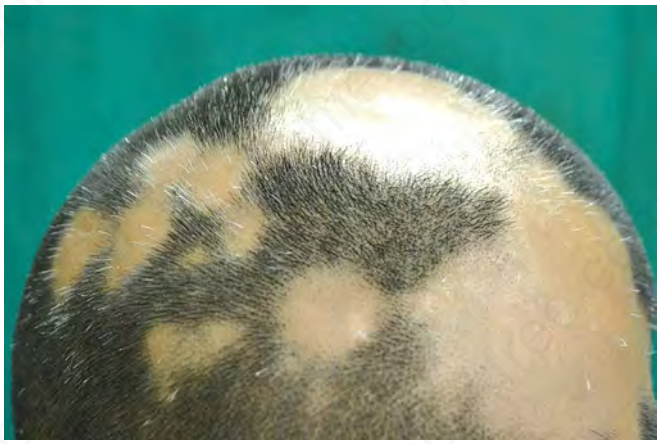


Fig. 4: Alopecia areata

suggests autoimmune origin; presence of lymphocytic infiltrate in and around anagen hair follicles is further evidence. Alopecia areata differs from other autoimmune diseases in that it does not result in complete loss of function of the target organ, but in a temporary switching off of hair follicle activity, which can return to normal. This suggests that the target may be a controlling growth factor or its receptor.

Treatment. 'Wait-and-see' approach can be tried.

i. *Corticosteroids:* (a) Systemic result in regrowth of hair in many cases, but most patients relapse. (b) Topical – may be effective. Folliculitis may be a side effect. (c) Intralesional – Injection around and within the lesions. Triamcinolone suspension 0.1 mL with each injection for maximum of 2ml. Reinjection at 4–6 weeks interval. Skin atrophy is a side effect; it can occur both at site of injection and in a linear manner following the direction of lymph flow. It should hence be used principally for accelerating regrowth in well-circumscribed and cosmetically disfiguring areas of hair loss.

ii. *Topical sensitizers:* Topical immunotherapy if more than 50% of scalp is involved. Repeated application of dinitrochlorobenzene (DNCB) and squaric acid dibutylester (SADBE). Side effects—Mild rash, pruritus, adenopathy and rarely erythema multiforme.

iii. *Anthralin* applied (0.1% to 0.4%) for night treatment) increased if tolerated to 1.0% once or twice a week for at least 6 months.

iv. *Minoxidil*: Topical application of 5%, not more than 25 drops bd for 12 weeks. Side effects – Hypertrichosis, irritation. It can be used in combination with other topical agents.

v. *Photochemotherapy* – PUVA therapy is combination of psoralen and UV light.

vi. *Topical immunomodulators* – Tacrolimus and Pimecrolimus have smaller molecular size which does not allow them to reach the site of pathology (i.e. the deep dermis).

2. ***Tinea capitis:*** Irregular patch of alopecia with scaling and broken off stubs of hair within the patch. Multiple patches may develop. Occasionally the patch may be inflamed (kerion). *Tr.* – Topical antifungal therapy is ineffective. Griseofulvin 10 mg/kg/day for 6 weeks or ketoconazole, itraconazole and terbinafine.

3. ***Lichen planopilaris:*** Lichen planus affecting hair follicles produces a patchy, scarring alopecia. Minute, purple papules may be seen around hair follicles at the edges of the patches. *Tr.* – Clobetasol topically. If not controlled 20–30 mg prednisolone p.o. for 6–8 weeks.

4. ***Folliculitis decalvans:*** Rare cause with pustules around follicles which heal with scarring and destruction of hair follicles. *Tr.* – Anti-staphylococcal antibiotics.

5. ***Skin diseases:*** That produce alopecia are discoid lupus erythematosus and morphea.

6. ***Trichotillomania:*** Produced by patient with psychiatric illness plucking her hair.

7. ***Traction alopecia*** **:** Produced by tying a tight pony tail. This is most prominent along hair margins because distant hair is subject to most traction.

Diffuse Alopecia

- The most common cause of diffuse hair loss is an androgenetic alopecia (common baldness, male-pattern alopecia). In men it causes typical temporal recession and thinning at the vertex ('Hamilton patterns' Fig. 5). In women a more diffuse hair loss is generally seen (Ludwig pattern).
- Other causes of diffuse hair loss include telogen effluvium, thyroid disease, severe iron-zinc, and protein deficiency. Drug-induced, e.g. cytotoxic agents such as vincristine, methotrexate, cyclophosphamide. These lead to hair thinning over the whole scalp in contrast to frontoparietal loss in androgenic alopecia.

Assessment of diffuse hair loss: It is important to examine the scalp to exclude inflammatory scalp disease or scarring alopecia.

- Detailed medical history
- Full blood count
- Serum iron and ferritin measurement
- Liver, renal and thyroid function tests

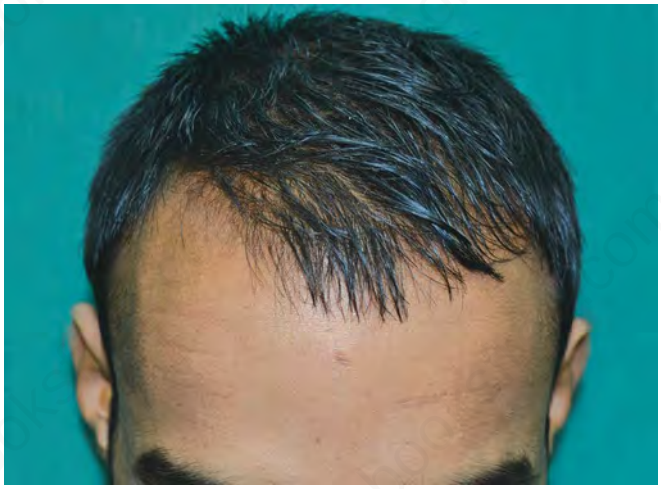


Fig. 5: Androgenetic alopecia

- Microscopy for hair (look for weathering, fractured hair caused by cytotoxic injury and any congenital abnormalities that may have made the hair shaft more susceptible to trauma).
- Trichogram, trichometry

Assessment of Women with Androgenic Alopecia

- Enquiry about amenorrhoea or oligomenorrhoea, which may suggest polycystic ovary disease
- Enquiry about galactorrhoea (elevated prolactin levels)

Examination for hirsutism and cutaneous virilism when the following investigations are necessary:

Prolactin
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Testosterone

Androgenetic alopecia is a genetically determined physiological change which involves a shortening of the anagen phase of the hair cycle and consequent increase in the proportion of telogen hairs. Structurally the terminal hair follicles transform into progressively smaller follicles ('miniaturization phenomenon').

Genetic basis. An autosomal dominant inheritance has been suggested, a multifactorial inheritance is possible.

Androgens. Men with syndrome of androgen insensitivity (e.g. 5 α-reductase deficiency) fail to develop temporal recession after puberty. A number of studies have failed to show a correlation between testosterone levels and baldness. In women baldness may be associated with elevated levels of circulating androgens; changes in hair patterns occur most commonly after menopause.

It appears that the essential inherited factor responsible for androgenic alopecia is the manner in which the follicles of the frontal and vertex regions of the scalp react to androgens.

Treatment

Non-surgical

Drugs

a. *Minoxidil,* a piperidino-pyrimidine derivative, is a potent vasodilator. Applied topically twice daily as a 2% solution results in conversion of some miniaturized hairs in about one third of men and 55% of women. Main side effect is local irritation. Five percent minoxidil may give better results but is not recommended in women because hypertrichosis may result due to its absorption.

b. *Cyproterone acetate* 50–100 mg may prevent further progression of hair loss. 2 mg of the drug with ethinyloestradiol may maintain the improvement in women in early stages of hair loss. Side effects: Lassitude, weight gain, breast tenderness, loss of libido and nausea.

c. *Spironolactone:* Subjective improvement may occur but patients complain of mood swings, irregular menses and breast tenderness.

d. *Flutamide* is a pure anti-androgen and there are short term reports of its effectiveness. It is potentially hepatotoxic.

e. *Finasteride* is a selective inhibitor of type 2 isoenzyme of 5 α-reductase, which converts testosterone to dihydrotestosterone. Dose of 1 mg/day p.o. results in increase in DHT levels in the scalp and serum. There are no significant side effects and no impairment of fertility. Because of its potential feminizing effect on male foetuses, it is contraindicated in pregnant women or those who may become pregnant.

f. PUVA prolonged therapy may induce regrowth of scalp and body hair.

Surgical

1. **Direct hair implant (DHI)** is a hair transplant technology, leaves behind no scar or stitches and is painless. The technique removes hair follicles one by one from the sides and back of the head and replants them with precision to restore hair line and density. It is performed under local anaesthesia. The implanted hair never falls and there is not much difference between the existing hair and the transplants.

2. **Hair additions:** It is a hair-bearing contraception that is added to the existing hair to give a 'fuller hair of head' appearance.
3. **Stem cell injection** that can cause local swelling and redness for 48 hours. They work by releasing proteins to coax hair growth. However if the hair roots are dead there is no technology that can revive it.

Telogen effluvium: As part of natural hair growth cycle, hairs in the telogen phase are shed from all areas of the scalp at a rate of up to 150 per day. Normally, these follicles then re-enter and no obvious hair thinning is apparent. If a large number of hair follicles enter catagen together, however, diffuse excessive hair loss is observed 2-3 months later. This may be seen following significant physical or emotional stress or after severe febrile illness. Once the stress passes, the hair usually returns to normal.

Other Causes of Diffuse Hair Loss

- High fever
- Hemorrhage
- Sudden starvation
- Malignancy
- Significant surgery
- Severe impairment of liver or kidney function
- Certain drugs
- Industrial or accidental exposure to certain chemicals

Slow onset of hair thinning is sometimes seen in absence of obvious hair shedding if hairs at the end of normal telogen fail to re-enter anagen. This is the pattern most often seen in iron deficiency anemia, hypothyroidism and hypopituitarism.

Secondary syphilis: The hair typically has a 'moth-eaten' appearance and tends to regrow after 4–6 months.

Chronic kidney failure: Mechanism is not understood. Hair loss is not reversed following dialysis.

Drugs: Drugs causing diffuse hair loss are listed in Table 7.

Chemical agents (e.g. hair dyes, bleaches, perm solutions) due to weathering of hair shafts.

Hirsutism

Hirsutism is growth of terminal hair on the body of a woman in a pattern similar to that which develops in healthy post-pubertal men. Hirsutism occurs in response to androgens and thus effects androgen dependant hairs. Hypertrichosis refers to growth of terminal hairs including non-androgen dependant follicles that is considered excessive for the site and age of the patient. Table 8 gives the causes of hirsutism.

Diagnosis

Physical examination: Pattern and severity of the hair growth, and associated androgenetic alopecia, acne vulgaris, obesity, acanthosis nigricans, deepening of the voice, increased muscle bulk, hypertension, galactorrhoea, striae distensae and cliteromegaly. Cliteromegaly is the most important sign suggesting virilization; if it is associated with a short history of hirsutism (< 1 year), it is highly suggestive of a tumorous cause.

Investigations

- In long-standing mild hirsutism with a regular menstrual cycle and no features of systemic virilism, no further investigation is required.
- Some patients with moderate hirsutism with or without menstrual irregularities have polycystic ovary disease, which can be confirmed by ultrasonography. Plasma testosterone levels may be helpful.
- Patients with severe hirsutism and virilization with a short history or very severe hirsutism with a long history, need investigation for an androgen-secreting tumour.

Table 7: Drugs causing diffuse hair

• Allopurinol	• Heparin
• β-blockers	• Lithium
• Borax	• Mercury
• Bromocriptine	• Pitressin
• Carbamazepine	• Retinoids
• Colchicine	• Sodium valproate
• Coumarins	• Thallium
• Cyclophosphamide	• Triparanol
• Doxorubicin	

Table 8: Causes of hirsutism

• Ovarian causes
– Polycystic ovary syndrome
– Ovarian tumors
• Adrenal tumors
– Congenital adrenal hyperplasia
– Adrenal tumors
• Cushing's disease
• Androgen therapy
• 'Idiopathic' hirsutism

Management

Cosmetic approaches include bleaching, shaving, plucking (e.g. waxing, sugaring), and depilatory creams. Electrolysis is the only permanent method of hair removal, but can be painful. Laser removal of hair takes long but is successful.

Systemic Antiandrogens

Cyproterone: (a) Low-dose therapy is given in the form of contraceptive pill 35 µg ethinyloestradiol and 2 mg cyproterone acetate taken for 21 days in every 28. (b) High-dose therapy: Cyproterone 50–100 mg for first 10 days only.

Spironolactone: 50–100 mg daily or cyclically (daily for 3 out of every 4 weeks). Spironolactone may feminize male foetuses; women taking the drug should avoid pregnancy.

Other agents: Flutamide and ketoconazole reduce hirsutism, but carry the risk of hepatic toxicity.

NAIL DISORDERS

The nail grows from the matrix and is supported by the nail bed until it reaches the free edge. At the proximal and distal margins, it is embedded in the nail folds. Local and systemic disease can alter the appearance and function of all four structures.

Local diseases: Common are:

- Fungal nail infections
- Periungual eczema
- Viral warts
- Tumors: squamous cell carcinoma and malignant melanoma

Systemic diseases:

- Vascular phenomena (e.g. splinter haemorrhages, cyanosis)
- Changes in nail growth as a result of general metabolic factors influencing nail matrix function
- Psoriasis

Nails in Systemic Disease

Nail Plate

1. **Grooves:** Beau's lines. Any severe illness may lead to a transverse linear depression on each nail. Because the average rate of fingernail growth is known, the position of the line indicates the approximate date of onset of the original illness. Also psoriasis, zinc deficiency.
2. **Ridges:** Longitudinal in lichen planus, RA. Impaired peripheral circulation may lead to longitudinal ridging and thinning of the nails.
3. **Pitting** – Psoriasis, alopecia areata, eczema, idiopathic.
4. **Thickening (tenting)** in pachyonychia congenita.
5. **Tachyonychia –** Grey rough surface affecting all nail plates (20-nail dystrophy).
6. **Colour changes:**

White – (a) *Punctuate spots* of no significance. (b) *Transverse bands* – Arsenic poisoning (Mees' lines), sometimes with palmar keratosis. (c) *True leukonychia* – Congenital or acquired, e.g. after systemic illness such as myocardial infarction, shock or ulcerative colitis. Opaque nails (opacity obscuring the lunula) in cirrhosis; also diabetes mellitus, cardiac failure. (d) *Half-and-half nails* – In chronic kidney failure. Two parts separated transversely by a well-defined line. The phenomenon disappears within 2–3 weeks of successful renal transplantation. (e) *Paired, narrow, white bands* – Hypoalbuminemia. (f) *Longitudinal white lines* – In Darier's disease (keratosis follicularis).

Splinter haemorrhages – Represent blood escaping from the longitudinal capillaries in the nail bed beneath the nail. The cause may be systemic or local. Trauma, rheumatoid arthritis and other collagen disease (reflecting the vasculitis), trichinosis, psoriasis, infectious mononucleosis, blood dyscrasias, cryoglobulinaemia, mitral stenosis sometimes, chronic mountain sickness, indwelling radial arterial catheters.

Linear pigmentation (Longitudinal melanonychia)- Coloured races, Addison's disease, pituitary tumours, cytotoxic drugs, vitamin B_{12} deficiency. In a single nail indicates underlying malignant melanoma.

Yellow nails – Yellow nail syndrome is characterised by increased transverse and longitudinal nail curvature, slow rate of growth and yellow discolouration of nails. It may be associated with lymphoedema, idiopathic pleural effusions, chronic chest infections and chronic sinusitis, tetracycline therapy, jaundice.

Green nails – Secondary pseudomonas infection in chronic paronychia.

Blue nails – Antimalarial drugs (e.g. chloroquine), Wilson's disease (restricted to lunula). Azure lunulae in argyria.

O-spots – Yellowish red discolouration in centre of nail. Typical of psoriasis.

Longitudinal brown streaks – (a) Subungual hematoma, often with red tinge. (b) Benign racial: often multiple. (c) Melanocytic naevus. (d) Malignant melanoma. (e) Drugs: minocycline, zidovudine. (f) Addison's disease.

(g) Multiple benign streaks with buccal pigmentation. (h) Frictional: On edge of toes, or occupational on hands. (i) Fungal infection. (j) Lichen planus. (k) Squamous cell carcinoma, eczematous dermatitis, pityriasis rosea, rheumatoid arthritis, Reiter's disease, SLE, dermatomyositis, sarcoidosis, diabetes mellitus (Rosenau spots), congenital pitting. (l) Peutz-Jeghers syndrome.

Red nails – Congestive heart failure (lunula).

Shiny nails – Indirect evidence of pruritus.

Changes in Shape

Koilonychia – Spooning of the nails in iron deficiency classically. Also in early infancy (temporary condition), hyperthyroidism, occupational, liver disease. High altitude (more common in upper limbs).

Clubbing – (See clubbing of fingers).

Onycholysis – Separation of the nail plate from nail bed sometimes in thyrotoxicosis. A form of clubbing termed (thyroid acropachy) occurs in Grave's disease.

Abnormalities of Nail Folds

1. *Proximal and lateral folds* – (a) Local infection or systemic disease such as collagen disease, psoriasis and Reiter's disease. (b) Pterygium – Prolongation of proximal nail fold into the nailbed, splitting and subsequent destruction of the nail in severe lichen planus.
2. *Cuticles* – Thickening and hyperkeratosis in dermatomyositis. These remit with lessening of disease activity.
3. *Vessels* – (a) Dilated and deformed capillaries in systemic sclerosis associated with Raynaud's phenomenon. (b) Loop appearance of vessels (resembling a glomerulus) in early lupus erythematosus.

Nailbeds

- Telangiectasia, erythema and thrombosed capillaries may be observed in connective tissue diseases.
- Cuticles may be frayed in nail biters, due to cosmetics and in connective tissue disease.

5. SKIN PROBLEMS IN PREGNANCY

Physiological changes in skin, nails and hair during pregnancy are listed in Table 9.

Table 9: Physiological changes in skin, nails and hair during pregnancy

• Hyperpigmentation
• Melasma
• Hirsutism
• Nail changes
• Vascular changes
• Increased eccrine activity
• Decreased apocrine activity
• Increased sebaceous activity
• Striae (vertical, dark red/purple)
• Pruritus gravidarum

Pruritus gravidarum is probably the most distressing physiological symptom and the aetiology seems multifocal. Oestrogens impair transport of bile to bile canaliculi, leading to increase in circulating bile salts, and prostaglandins reduce the threshold for pruritus. Liver function tests should be done to exclude cholestasis of pregnancy and common skin disorders. Some skin disorders improve with pregnancy (e.g. atopic eczema, acne vulgaris, hydradenitis suppurative, psoriasis), but a greater number tend to deteriorate (e.g. SLE, infections, such as candidosis, viral warts and herpes simplex).

SPECIFIC DERMATOSES OF PREGNANCY

1. **Polymorphic eruption of pregnancy** is the most common rash in pregnancy. There is an association between excess maternal weight gain and increased newborn weight. Most patients are primigravida and the rash most commonly develops in the third trimester or postpartum, and lasts on an average for 6 weeks. Lesions begin on lower abdomen within striae. The umbilicus is spared. The upper inner thighs are also affected. Pruritic urticarial papules develop which coalesce to produce plaques, vesicles, target lesions and polycyclic wheals.

   Tr. – is symptomatic. Moderately potent corticosteroids are usually more effective than antihistamines in relieving pruritus.
2. **Pemphigoid gestationis** classically presents as a bullous disorder during pregnancy and puerperium. It can also be associated with choriocarcinoma, trophoblastic tumors and hydatidiform mole. It is a serious condition and the neonate may develop severe bullous eruption at birth. The disease also produces small-for-date babies because of placental insufficiency.

   Pemphigoid gestationis usually develops in the second or third trimester or in the immediate puerperium. It often recurs in subsequent pregnancies with more severe disease.

   Immunofluorescence performed on frozen sections of uninvolved skin and serum is the best diagnostic test for the disease and is positive in all cases.

   Tr. – Mild cases respond to moderately potent topical corticosteroids but systemic corticosteroids are

generally required (e.g. 20–40 mg for less severe cases, 40-80 mg for severe cases, in a reducing course). A postpartum flare invariably occurs, requiring a higher dose. Severe cases may require plasmapheresis or the luteinizing hormone-releasing hormone analogue goserelin, which induces a reversible chemical oophorectomy. However, the drug can only be used in the postpartum phase.

3. **Prurigo of pregnancy** usually begins in the third trimester and often persists for several months postpartum. The lesions are grouped excoriated papules on extensor surfaces of limbs, abdomen and shoulders. Fatal prognosis is poor.

   Tr. – Topical application of moderately potent corticosteroids and if necessary sedating antihistamines.

4. **Pruritus folliculitis of pregnancy** is thought to be a pruritic hormonally induced acne. Clinical appearances are of a folliculitis similar to the monomorphic acnes seen in patients taking corticosteroids or progestogenic steroids.

Clinically, the diseases is characterized by grouped lesions consisting of urticarial papules and polycyclic wheals. Most patients first develop a rash in the umbilicus that later spreads to the thighs, palms and soles but seldom involves the face or oral mucosa. Target lesions, vesicles and large tense bullae subsequently develop and closely resemble bullous pemphigoid.

Tr. – Topical application of 1% benzoyl peroxide and 1% hydrocortisone cream.

Chloasma (melasma, pregnancy mask) is an increase in epidermal or dermal pigmentation that occurs during pregnancy. The hypermelanosis affects the cheeks, forehead and chin and becomes more marked following sun exposure. It occurs in later half of pregnancy or postpartum. Grouped, well-defined, 2–5 mm, light to dark brown macules tend to coalesce in the centre resulting in bigger brown patches. Macules remain more or less discrete at the periphery, which become irregular in outline.

Treatment – Avoidance of sunlight and application of a sun screen. Hydroquinone cream applied over a long time may help to lighten the patches, but total clearing is rare. Chemical peeling, Laser therapy are also used.

EFFECTS OF PREGNANCY ON PRE-EXISTING SKIN CONDITIONS

Psoriasis. Effects are variable. A rare form of generalized pustular psoriasis (impetigo herpetiformis) may be seen.

Acne usually improves in pregnancy, but may deteriorate. Erythromycin topically or systemically is a safe treatment option.

Atopic eczema. Effects are variable. A few women develop prurigo of pregnancy. Breast feeding may be desirable in atopic women because it may reduce the infant's risk of developing eczema.

6. TUBERCULOSIS OF THE SKIN

Cutaneous infection with *M. tuberculosis.* Clinical appearance varies with mode of infection, which can be metastatic or from draining lymphnodes (Table 10).

LOCALIZED FORMS OF CUTANEOUS TUBERCULOSIS

1. **Primary tuberculous complex (tuberculous chancre)**, is found usually in those children and young adults who have not contacted TB. Lesion is a nodule which, through central necrosis, breaks down to form an indolent indurated ulcer. It occurs on the face, genitals and limbs. Adjacent lymphadenopathy. Microscopic examination shows typical tubercular histology.
2. **Lupus vulgaris** is the most common type of inoculation tuberculosis. These patients have a moderate to high degree of immunity against TB bacilli.

   The primary lesion is a reddish-brown pin-head sized nodule. A number of these nodules may coalesce to form a dark-red inflammatory patch which slowly extends peripherally (Fig. 6).

   The patches are irregular in shape and vary in size, but are always elevated above the surface and studded with minute brownish nodules. When the patch is examined by diascopy, the nodules assume the 'apple jelly' colour from which they derive their name. The disease spreads slowly over many years with resultant scarring.

   Sites – Begins in childhood or adolescence upon the face, the cheeks and nose being most commonly affected. Also buttocks, thighs.

Table 10: Tuberculosis of the skin

• Primary inoculation tuberculosis (tuberculous chancre)*
• Reinoculation TB – Lupus vulgaris, tuberculosis verrucosa cutis
• Contiguous spread from underlying organs – Scrofuloderma
• Haematogenous spread – Miliary tuberculosis
• Autoinoculation TB, e.g. perioral TB in pulmonary tuberculosis or periurethral in renal tuberculosis

*Due to direct inoculation of the skin through minor cuts, abrasions, insect bites or other wounds and is analogous to the primary complex of pulmonary TB.

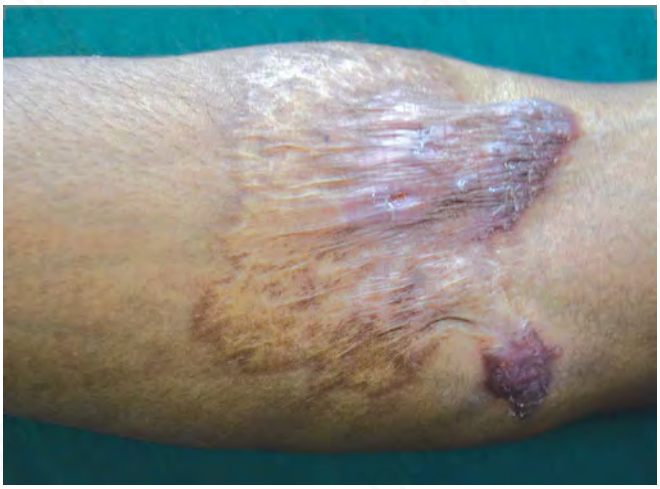


Fig. 6: Lupus vulgaris

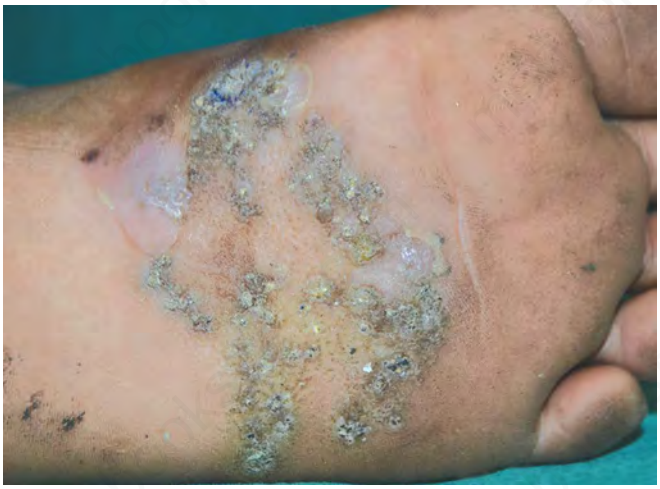


Fig. 7: Tuberculous verrucosa cutis

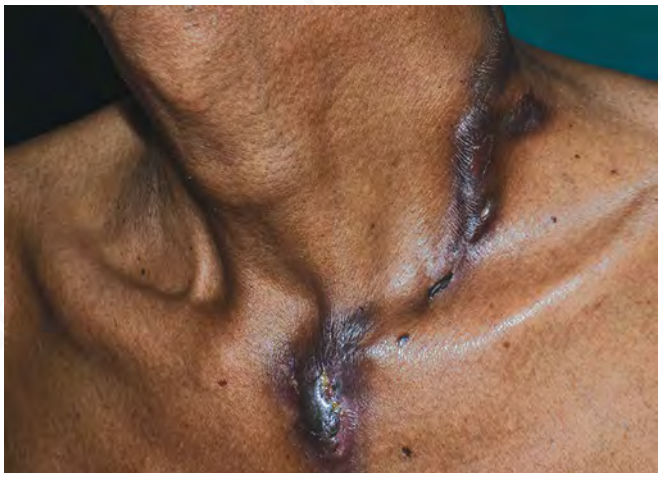


Fig. 8: Scrofuloderma

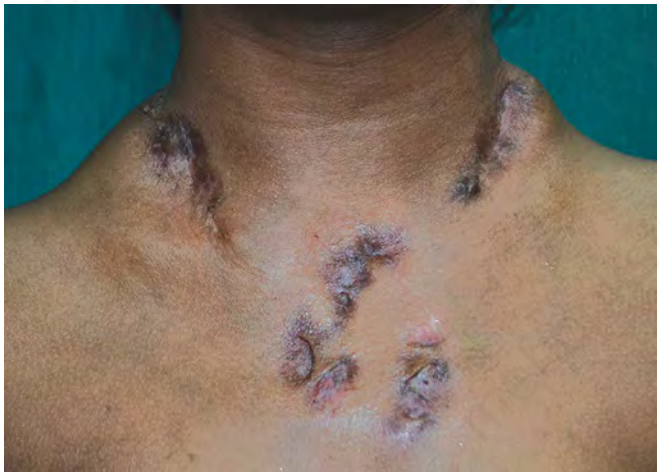


Fig. 9: Scrofuloderma

Clinical types or variants:

- Atrophic or smooth, composed mainly of scar tissue and containing many 'apple-jelly' nodules.
- Hypertrophic type – keratotic verrucose surface of the plaque (Fig. 7)
- Ulcerative resembling scrofuloderma

3. **Tuberculous verrucosa cutis** (Anatomist's wart, postmortem wart). The bovine bacillus is usually responsible.

   A reddish papule or small nodule appears at the site of inoculation. It tends to heal at one end and progress at the other.

   In time papillomatous changes occur and a dusky-red, wart-like lesion results.

   Sites: Knuckles and or back of hands, i.e. those parts most exposed to abrasions or cuts.

4. **Scrofuloderma** (Figs. 8 and 9) is the result of direct extension from subcutaneous tuberculous structures, commonly lymph nodes, bones or joints. The overlying skin breaks down with resulting sinuses discharging serosanguinous fluid. The lesions heal with puckered scarring.

   Skin covering the affected organ becomes purplish and stretched and finally yields, giving rise to one or more sinuses through which a seropurulent fluid and caseous matter is discharged. Later ulcers form around these sinuses with irregular, undermined bluish borders. The ulcerative process may become extensive and pockets and fistulae are common. The disease may persist for years with disfiguring scarring.

   Scrofuloderma. Multiple discharging sinuses with underlying matted lymphnode swellings in the neck are typical.

5. **Tuberculosis cutis orifacialis** (acute tuberculous ulcer) affects the skin at mucocutaneous borders of body orifices and is secondary to TB of internal organs particularly the lungs. The ulcers are soft, shallow, rounded or oval, discrete, indolent with irregularly undermined edges and thin yellow crusts. Tongue is the most common site of involvement, other sites of involvement include floor of mouth, soft palate, anterior pillars and uvula. Secondary involvement of the draining lymphnodes may occur.

   Sites – Oral, anal and genital regions. They are painful and healing is slow. Healing may not take place without effective AKT because of poor immunity of the patient.

6. **Tuberculides.** Group of diseases, probably a hypersensitive reaction to *M. tuberculosis,* characterized by evidence of manifest or past TB, absence of bacilli in skin biopsy specimen and culture, response to anti-TB treatment. The clinical entities are (i) Lichen scrofulosorum, (ii) Papulonecrotic tuberculide (papules with central necrosis which come out in crops and symmetrically distributed on face or extremities) (Fig. 10).

7. **Tuberculosis miliaris acutus** is a disease neither tuberculide nor a sarcoid. It is a disease of childhood, as a concomitant of exanthematous miliary TB and usually follows measles, whooping cough or scarlet fever. Due to breaking down of a tubercular lesion and the subsequent embolic spread, TB bacilli are disseminated widely through the blood stream. Lesions are generalized and papular, soon becoming ulcers. Tuberculin test may be negative since patient's resistance is low.

8. **Tuberculous gumma.** Haematogenous dissemination from a tuberculous focus can result in a gumma seen mainly in immunocompromised children. The lesion is initially a subcutaneous nodule which breaks through the skin to form an ulcer with undermined edges.

9. **Primary tuberculous infection of glans penis.**

7. INFECTIONS

ECTOPARASITE INFECTIONS

SCABIES

A contagious disease caused by a mite, *Sarcoptes scabiei*, is spread through contact with infected individuals, or rarely through contact with infected clothes, bed linen or towels.

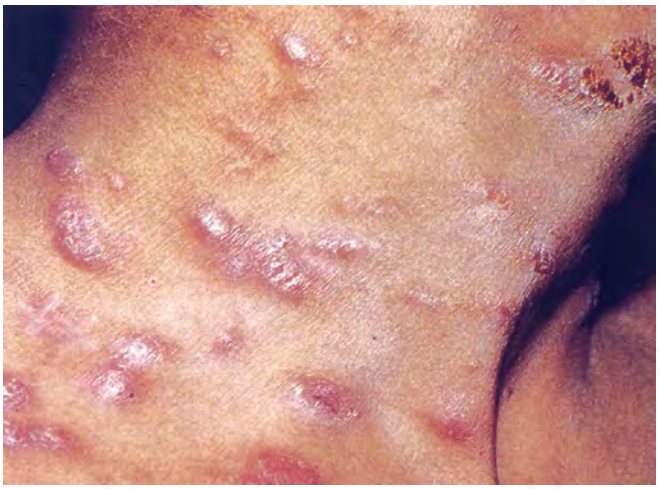


Fig. 10: Tuberculids

Life Cycle

The fertilized female excavates a sloping tunnel (burrow) in the stratum corneum, depositing eggs and then dying in the burrow. The larvae emerge from the eggs after 3–7 days, wander to the skin surface and form shallow pockets in the horn of the original or a new host, and reach maturity 14–17 days after the eggs were laid. Copulation occurs in the pocket and the female excavates her burrow, while the male soon dies. In children, palmar involvement is common. Inspite of widespread manifestations, total number of mites is 10–15 ovigerous females.

Clinical Features

Pruritus – The sole complaint is severe itching worse at night. Itching starts two to four weeks after the contagion, this time lag being required for the development of lesions other than the burrow.

Burrow – It is the diagnostic sign of scabies. It is a slightly elevated greyish tortuous or dotted line in the skin ridge. It represents a tunnel made by the female mite in the horny layer of the skin in which to lay her eggs. Burrows are best seen in the soft parts of the skin, such as the hands, feet, penis and scrotum.

Scratching destroys the roofs of the barrows and mites, keeping the population under control.

Rash – During the initial phase of infection, the host is asymptomatic but after 4–6 weeks a hypersensitivity response to mite antigen occurs and an itchy rash develops. The rash comprises tiny inflammatory papules which occur predominantly in the interdigital folds (Fig. 11) of hand, around the axillae, in the periareolar regions, on the

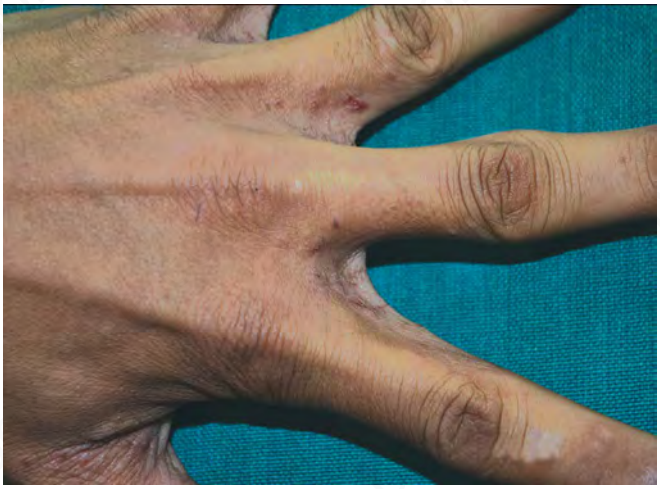


Fig. 11: Scabies with autosensitization

abdomen (particularly the periumbilical region) and on the buttocks and medial aspects of thighs, legs and feet. In males inflammatory papules on penis and scrotum, which are pathognomonic of scabies.

Complications

1. ***Eczematization.*** It is common in infants and young children. Involved areas of the extremities and trunk show erythema, oedema, vesiculation, oozing and crusting. The face is commonly involved in infants.
2. ***Secondary infection.*** Secondary bacterial infection (Strepto or staphylococcal) may occur in case of untreated scabies. The existing lesions turn into pustules and even bullae which when they burst are covered with yellowish crusts. Scratching results in excoriations.
3. *Id eruption.*
4. *Urticaria.*
5. *Contact dermatitis to antiscabietic drugs.*

Variants of Scabies

1. *Scabies in the clean* – These have fewer lesions, some of which are at atypical sites, but cause severe itching.
2. *Scabies incognito* – occurs in persons treated with steroids.
3. *Nodular scabies* – Urticated papules and occasional vesicles are thought to be a hypersensitivity reaction. Red pruritic nodules are often found on the genitals. Scabietic nodules often do not contain mites.
4. *Genital scabies* – In males there are inflammatory papules on the penis and scrotum which are pathognomonic of scabies.
5. *Norwegian (crusted) scabies* is an uncommon subtype in which a deficient immune response allows large numbers of mites to multiply. The crusts and psoriasisform scales, loaded with scabies mite affect the hands, scalp, face and trunk. Itching may be minimal. Susceptible individuals are only marginally immunosuppressed and may simply be elderly, or pregnant.
6. *Scabies in AIDS* is more severe and extensive with involvement of face and scalp.
7. *Paraphimosis* may be a complication in children.
8. *Immunological sequelae* from associated streptococcal infection may manifest as glomerulonephritis or rheumatic fever.
9. *Animal transmitted scabies* can be acquired from animals, e.g. dogs. Clinical pattern is quite different from that produced by human bite. Lesions are most common on forearms, lower chest, abdomen and thighs, areas most exposed to the mite, by the person carrying the affected pet. Burrows are conspicuous by their absence. The infestation has a short incubation period.

Diagnosis. History of similar illness in other members of the family. Characteristic distribution pattern of lesions. Itching worse at night. Diagnosis is made by deroofing a burrow with an oil-coated needle and examining scrapings for mites and their ova microscopically.

Differential Diagnosis – Similar signs are found with papular rashes from fleas, including papular urticaria; also atopic skin lesions in young children with maximal lesions on extremities; generalised pruritus, delusions of parasitosis.

Management

1. All the family members should be treated at the same time.
2. The clothes, bed linen and towels should be disinfected.
3. Secondary infection should be treated first.
4. Specific therapy – The patient must bathe and scrub the body with a brush to lay open the burrows. After the bath, the skin is dried and the scabicide applied from neck to toes (Table 11).

Treatment of crusted scabies is as for ordinary scabies, but several applications of scabicide are necessary. Oral Ivermectin may be useful in resistant cases.

Treatment of Complications

Bacterial infections – Antibiotics like erythromycin or roxithromycin. Topical antibiotic, e.g. mupirocin or framycetin.

Table 11: Specific therapies for scabies

Drug	*Regimen*	*Adverse effects*
Permethrin 5% dermal cream	Treatment of choice Single application washed off after 12 hrs	Nil significant
Benzyl benzoate 20% emulsion	2 or 3 applications within 24 hrs, on successive days or at intervals of 1 week	Irritant
Gamma benzene hexachloride 1% lotion and cream	Applied for 8–12 hrs and then washed off	Not to be used in pregnant women. Neurotoxicity in infants or young children or those with seizure disorders if overuse
Malathion 0.5% in aqueous base	2 applications separated by interval of 7 days	Nil significant
Crotamiton 10% cream and lotion	Twice daily for 5 days	Nil
Precipitated sulphur 5% gel or cream	3 night washed off after last application	Advantage of antipruritic action
Ivermectin 20 µg/kg	Single oral dose	Not to be used in underweight children, pregnancy

Eczematization – Condy's solution compresses in oozing stage followed by topical steroids. Later treatment of scabies.

Nodular scabies – Topical or intralesional steroids.

PEDICULOSIS (LICE)

All lice feed on blood, using piercing mouthparts. The lice that parasitize humans are:

Head lice (pediculosis capitis). Head louse infection is acquired by head-to-head contact with an affected individual. Spread of infection is predisposed to by poor hygiene and overcrowding. Also boarding schools.

Clinical manifestations – Head itching is the principal manifestation. Secondary bacterial infection may occur due to scratching, and concomitant head louse infection must always be considered in cases of scalp impetigo. Hair with empty egg cases are in the postauricular and occipital regions. Posterior cervical lymphadenopathy is a common presentation.

Adult lice and nymphs may be detected by combing wetted hair with a fine-toothed comb.

Treatment

Insecticides (See table). Lotion preparations are preferred because these expose the lice and eggs to a higher concentration of insecticide for a longer period of time than shampoos. They should remain on the scalp for 12 hours. Treatment should be repeated after 7–10 days.

Vinegar or formic acid is used to remove the glue to hold the mite firmly to the hair shaft. Other family members should be treated if there is evidence of infection.

Manual removal of eggs is an alternative to chemical means. Regular combing of wetted hair with a fine toothed comb is time-consuming but can effectively eliminate louse infection.

Pediculosis corporis (Clothing lice). These parasites are correctly designated because they live and lay their eggs on seams of clothing and visit the body only to feed.

Itching is the main complaint and the body is covered in excoriations, and the skin is often hyperpigmented in those who harbour lice for a long period (vagabond's disease). Since lice cause irritation, there may be small red papules with a tiny central clot. Lice and eggs should be looked for in the clothing.

Treatment – The clothing and not the patient requires treatment. High temperature laundering is effective means of killing both lice and eggs.

Pediculosis pubis (Crab lice). The louse adapted to living in hair of a particular density, apart from the pubic area, it may be found on the scalp margins, eyelashes and beard, axillary hair, hair on the trunk and limbs and the perianal regions. It is transmitted by close physical, usually sexual contact.

Itching, mainly in the evening and nights is the principal symptom. Close inspection of hairy areas reveals lice grasping hair close to the skin surface, eggs attached to hair shafts and rust-coloured louse faeces on the skin and hair.

Treatment – Malathion and carbaryl are effective. Treatment of choice is an aqueous preparation, alcohol based preparations irritate delicate areas such as the scrotum. All hairy areas should be treated, and treatment repeated after 7–10 days.

Eye lashes should be treated with white soft paraffin applied three times daily for 2–3 weeks.

Treatment of pediculosis

See Table 12 for the treatment of pediculosis.

8. CUTANEOUS FUNGAL INFECTIONS

Fungal infections are caused by non-photosynthetic vegetable parasites called fungi. Depending on whether the species resides in soil, animals or human beings, it is said to be geophilic, zoophilic or anthrophilic. Infection with zoophilic are often suppurative. Common cutaneous mycoses and sites of infection are given in Table 13.

SUPERFICIAL MYCOSES DERMATOPHYTOSIS (RINGWORM)

There are three genera of dermatophytes: *Trichophyton, Microsporum* and *Epidermophyton*. They are grouped according to their natural habitat as geophilic (soil), zoophilic (animals), and anthrophilic (humans).

Transmission may be indirect (via desquamated epithelium) or direct through bodily contact.

Predisposing factors – Warm, humid climate, poor nutrition and hygiene, obesity, diabetes mellitus and debilitating illness.

Common symptom is pruritus in all types of dermatophytosis. In AIDS patients, dermatophytosis leads to widespread or atypical infections and rapidly spreading white onychomycosis involving the whole nail plate.

Tinea Capitis

1. *Non-inflammatory type* – (a) Partial or complete round or oval shape areas. (b) Black dot patch–Scaly areas of alopecia with black dots due to broken off hair from endothrix infection. (c) Grey patch, dull grey hairs with scaly alopecia patch. (d) Seborrhoeic dermatitis type with dry scaling.
2. *Inflammatory type* – (a) Kerion due to zoophilic fungi. Boggy painful inflammatory swelling with exudative folliculopapules, with fallen off or easily pluckable hair. (b) Favus – Circular yellow crusts (scutula) around hair follicles. Patients have a "mousy" odour.

Table 12: Treatment of pediculosis

Type	*Therapy*	*Comments*
Capitis Corporis Pubis	GBH 1% lotion or Permethrin 1% lotion or 5% cream Malathion 0.5% High temp. laundering or wash clothes in boiling water and press with hot iron Application of permethrin or GBH to all affected hairy areas	To be applied overnight Antibacterials if secondary infection Clothing can be treated with GBH Treat all sexual contacts of infected individuals if possible

Tinea Barbae

Is usually found in adult males. It is acquired from a barber's instruments, or from animals. They commonly are observed on the chin, neck and maxillary areas. Hair in the affected areas can be easily pulled out. Resolution leaves behind scarring and alopecia.

- *Superficial or sycosiform type* – Diffuse erythema with perifollicular papules and pustules. Anthropophilic organisms (T. rubrum and T. violaceum) invading the endothrix are the cause.
- *Circinate or spreading type* – with a vesiculopustular spreading border, spreading peripherally and clearing in the centre.
- *Non-inflammatory type* – starts as a small erythematous papule surrounding a hairy shaft, later on these patches of partial alopecia, circular or oval in shape, showing numerous broken off hair, dull grey or lustreless.
- *Inflammatory type* – Lesions are nodular and boggy, often associated with seropurulent discharge.

Tr. – Systemic antifungal, e.g. griseofulvin 500–1000 mg/d. Topical antifungals, wet compresses and debridement of crusted lesions.

Tinea Faciei

Annular, shiny lesion due to lack of scaling.

Table 13: Common cutaneous mycoses and sites of infection

Superficial
• Dermatophytosis – Tinea corporis, tinea pedis, tinea capitis
• Superficial candidosis – Cutaneous, oropharyngeal, vaginal
• *Malassezia* infections – Pityriasis versicolor, seborrhoeic dermatitis, *Malassezia* folliculitis
• Others (e.g. black piedra, white piedra, Scytalidium infections)
Subcutaneous
• Mycetoma
• Chromoblastomycosis
• Sporotrichosis
Site of involvement
• Scalp: Tinea capitis
• Beard area: Tinea barbae
• Face: Tinea facie
• Groin and buttocks: Tinea cruris
• Body: Tinea corporis
• Hands: Tinea manuum
• Feet: Tinea pedis
• Nails: Tinea unguium

Tinea Corporis

Ringworm of the glabrous skin can occur anywhere on the body. It is caused most often by *Trichophyton* species.

Description – The lesion starts as a papule which spreads ring-like peripherally with central clearing. The lesions are usually circinate (Fig. 12) with an active border consisting of vesicles and scaling.

Distribution – Waistline, axillae, buttocks, other parts of the trunk and extremities but not palms, soles and groins.

D.D. – (a) Tuberculoid leprosy where minimal infiltration in the periphery mimics the active border of Tinea circinata. (b) Intertrigo with scabies with lesions in flexural and moist sites which are also sites of predilection for T. circinata. (c) Impetigo circinata particularly in children. (d) Tinea versicolor. (e) Psoriasis. (f) Secondary syphilis.

Complications – (a) Eczematisation: Due to scratching, skin can get inflamed with redness, oozing and crusting. (b) Secondary pyogenic infection. (c) Id reaction – An allergic eruption to the antigenic reaction, particularly on palms and soles. (d) Dissemination in immunocompromised individuals.

Tinea cruris – Ringworm of the groins and upper and inner parts of the thighs. Obesity, moisture, warmth and friction are the important factors for its existence. It spreads to the buttocks, and lower abdomen.

Tinea Pedis

It is very pruritic, may be vesicobullous in nature, and occurs on the instep and plantar surface of the foot. The fungus is acquired from the flooring, shoes and socks or communal baths. *Between the toes*, it causes maceration especially of the space between the fourth and fifth toes, and may result in fissuring and secondary infection. Sometimes the only evidence is a chronic, hyperkeratotic scaling eruption with minimal infiltration.

Four types with overlap:

- Chronic intertriginous type
- Chronic papulosquamous pattern – Inflammatory and patchy or diffuse moccasin-like scaling over soles
- Vesicular type near instep and mid-anterior plantar surface
- Acute ulcerative variant with maceration

Tinea manuum affecting the hands, is usually caused by *T. rubrum*. Inflammation is often minimal. The palm becomes dry with mild scaling which is most obvious in the palmar creases.

Tinea Unguium

Is a dermatophyte infection of the nail plate with brittleness, friability and thickening of the nail. The infection usually starts at the free margin and lateral border of the nails and progresses towards the nail fold. There may be a tinea infection on other parts of the body.

Tinea Incognito

Topical and/or systemic steroids may mask inflammatory features of tinea.

INFECTIONS

1. *Onychomycosis* includes all infections of the nail caused by any fungus including non-dermatophytes and yeasts (Fig. 13).

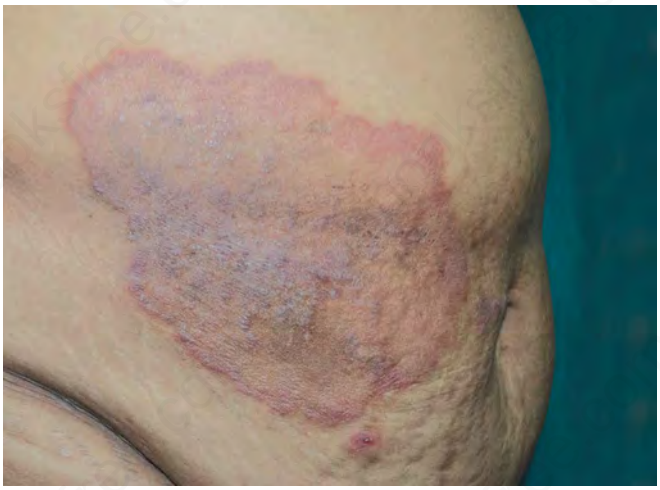


Fig. 12: Tinea corporis

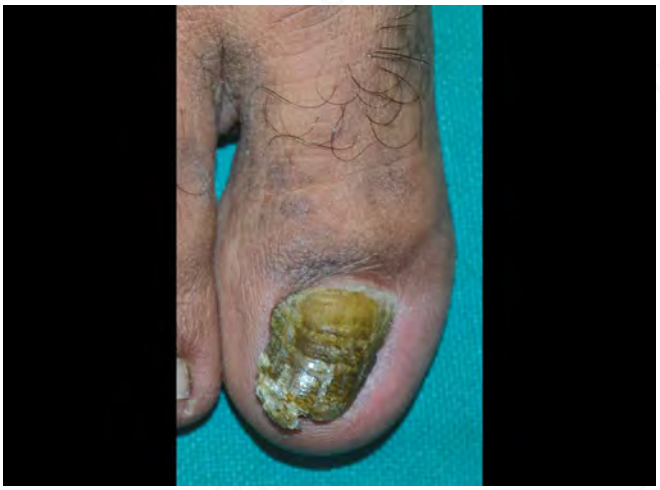


Fig. 13: Onychomycosis

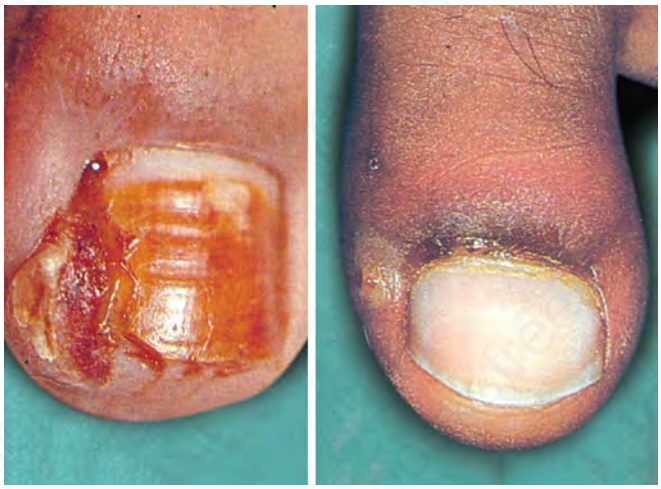


Fig. 14: Acute paronychia

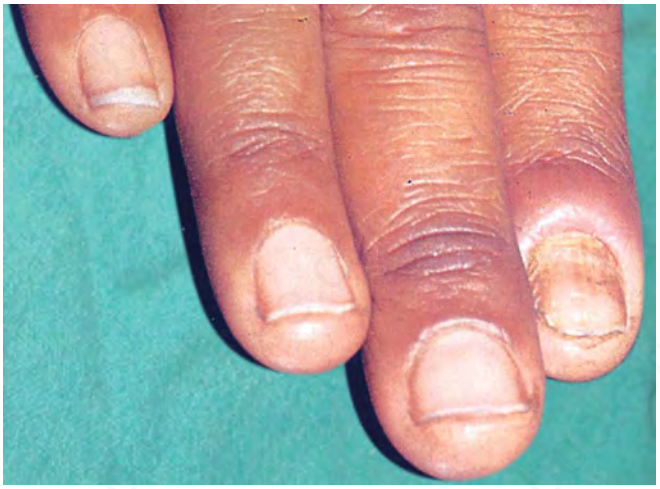


Fig. 15: Chronic paronychia

Cl. Fs. – Nail plate is yellow and thick with subungual hyperkeratosis, which is friable: Toe nails are more frequently involved.

2. *Paronychia* – is inflammation of nail folds.
   a. Acute paronychia – Swollen, tender red nail fold with visible pus under it (Fig. 14).
   b. Chronic paronychia – Inflammatory dermatosis of nail folds with secondary effects on nail matrix and nail growth (Fig. 15). Predisposing factors – Network as in domestic workers, house wives, DM, candidal vulvo vaginitis.

Cl. Fs. Swollen nail head. Adjacent nail plate becomes ridged and discoloured.

Laboratory Diagnosis

Dermatophytes are seen as hyphae and spores in skin scales (obtained by scraping with a scalpel) or in nail or hair samples, and mounted in 10% KOH for 20 minutes. These can also be cultured on Sabouraud's medium, or on Dermatophyte Test Medium (DTM).

Management

Prophylaxis

1. Patients who sweat a lot should change their clothes frequently, wear cotton socks and avoid synthetic material.
2. Clothes, especially the underwear, and towels should be boiled in hot water.
3. Footwear should be of the open type permitting sufficient aeration.
4. Intertriginous areas should be kept dry with powders, e.g. talcum or antifungal powder.
5. Shampoo the hair immediately after visit to the barber's shop.

Specific treatment

1. *Topical antifungal agents* –

   Clotrimazole – Cream 1%

   Miconazole – Cream 2%

   Econazole – Cream 1%

   Ketoconazole – Cream 2%

   Oxiconazole – Cream, lotion 1%

   Sulconazole – Cream, solution 1%

   Terbinafine – Cream 1%

   Butenafine – Cream 1%

   Luficonazole – Cream 1%
2. *Wet compresses* – Blisters, and pustules should be broken down and treated with wet compresses of 1:4000 solution of potassium permanganate, or Burrow's solution (Aluminium acetate) diluted 1 in 15.
3. *Keratolytic agents* – are best used on palms and soles, lesions which require softening and exfoliation. Half strength Whitfield ointment is applied b.d.
4. *Surgical avulsion* – of infected nails together with systemic griseofulvin therapy for infection of the nails.

Systemic Therapy

See Table 14 for the systemic therapy of fungal infections.

In Tinea imbricata, concentric polycystic rings become confluent to form a bizarre pattern covering most body surfaces. T. rubrum can produce large, scaly, minimally inflammatory plaques with little marginal accentuation.

Table 14: Systemic therapy of fungal infections

Drug	*Dose*	*Duration*	*Comments*	*Adverse effects*
Griseofulvin	Adult 500 mg o.d. Child 10 mg/kg with food	Corporis 4 wks Capitis 2 mths Pedis 3 mths Finger nails 5-6 mths Toe nails 18 mths	Not effective in versicolor or candidiasis	Not common–Headache GI irritation, skin rash, photosensitivity
Terbinafine	250 mg o.d.	Finger nail 3 mths Toe nail 6 mths	Not effective in candidiasis, contraindicated with ketoconazole	GI symptoms, rash, taste disturbances
Ketoconazole	200–400 mg o.d.	Corp. 3–6 wks Cap./man/pedis 6–8 wks Fin. nail 6 mths Toe nail 1 yr	LFT monitoring, Contra. with terfenadine because of CVS effects	Hepatotoxicity Anaphylaxis Interference with steroid synthesis and with oral anticoagulants
Itraconazole	100–200 mg/d	Pity. 5 days Corp. 5 days Fin. nails 3 mths Toe nails 4 mths Cap/man/pedis	Safer than Ketoconazole Level of drug is higher in epidermis than plasma, therapeutic conc. up to 4 wks after stopping. Hence intermittent therapy 200 mg x 7 days once a month	Nausea, vomiting, elevated liver enzymes
Fluconazole	150 mg once a week. 400 mg stat at night for tinea versicolor	3–7 days	With food to avoid gastritis. Effective in candidiasis	Nausea, vomiting, diarrhoea, abdominal pain Skin rash

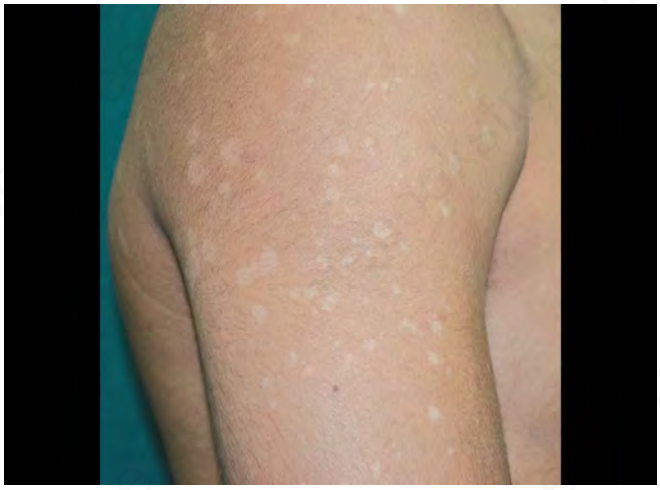


Fig. 16: Pityriasis versicolor vitiligo

MALASSEZIA INFECTIONS

Malassezia are common surface commensals of greasy skin sites, such as scalp and face. They are associated with pityriasis versicolor, seborrhoeic dermatitis and a form of folliculitis.

PITYRIASIS (TINEA) VERSICOLOR

It is the most superficial fungus infection produced by Malassezia furfur, characterized by scaly white or brown patches, asymptomatic in nature (Fig. 16).

Description – Asymptomatic macules and patches of various sizes and shapes, yellow, white or brown in colour.

Distribution. Occur at any site in the body commonly on the trunk. The lesions are scaly and easily detected when the part is abraded with a pin. It is usually seen in people who sweat excessively. The patches resemble vitiligo, but presence of scaling is typical and the lesions are never totally lacking in pigment.

Scales can be made more obvious by striking the lesions with a blade or knife (*Scratch sign*). At times the lesions may assume different colours such as reddish brown, dark brown or even black (hence the term versicolor).

Diagnosis – (a) The patches fluoresce golden yellow, under Wood's light. (b) Scraping the lesions and mounting them in 10% KOH solution reveals clusters of spores and short broad hyphae, resembling 'spaghetti and meat balls'.

Management

Any of the following may be used locally:

A. ***Topical therapy –***
   1. Sodium thiosulphate – in a 20 per cent solution applied, allowed to dry and left in place before rinsing, for 5–7 days.
   2. Ketoconazole 2% shampoo applied to the skin, allowed to dry and left on overnight as a single dose or daily for 3 days.
   3. Selenium sulphide – 2.5% as shampoo applied to the skin for 5–10 minutes once daily for 3–4 weeks before bath.
   4. Antifungal creams or solutions including imidazoles, tolnaftate.
   5. Zinc pyrithione shampoo applied for 5 minutes daily for –2 weeks.

6. Keratolytic creams or lotions.
7. Retinoic acid cream.

B. ***Systemic therapy*** – Oral antifungals, e.g. ketoconazole 200 mg o.d. × 14 days or Fluconazole 200 mg o.d. × 10 days if persistent or recurrent.

Seborrhoeic dermatitis – is a chronic inflammatory dermatosis affecting areas rich in sebaceous glands, such as the face, nasolabial folds, the front of the chest and the scalp (dandruff). Severe seborrhoeic dermatitis is particularly common in patients with AIDS or chronic neurological conditions such as Parkinson's disease.

Distribution – Seborrhoeic regions of young adults who have active sebaceous glands – Commonly on the trunk, also axillae, groins, proximal extremities and occasionally face and inframammary folds in females.

Clinical Features

Infants: Seborrhoeic dermatitis usually begins within first few days or weeks after birth, as greasy scaling in the scalp (cradle cap). Small, round or oval, erythematous, scaly lesions are seen on the face and napkin area. Apart from the face, retroauricular areas and temples are also affected. Most cases clear within a few weeks.

Adults – Lesions may be seen on the hairy skin of the scalp, face (especially eyebrows and nasolabial folds), on and behind the ears, presternal and interscapular regions, flexures (inflammatory folds, axillae, groins, anogenital folds) and periumbilical.

Scalp – Dandruff is an exaggerated loss of keratinized cells from the surface of the scalp and itchy dandruff is considered a manifestation of seborrhoeic dermatitis. Later perifollicular erythema and scaling form well-defined patches which coalesce and cover the scalp to extend beyond the forehead hairline as the 'corona seborrhoea'. Behind the ears there is erythematous greasy scaling, and a crusted fissure may develop in the retroauricular fold.

Face – Erythema and scaling involve nasolabial folds. Blepharitis occurs in the form of a red eyelid margin covered by small scales. Eventually small ulcers covered with crusts form, leading to destruction of eyelid hair. In men the beard area is affected with lesions similar to those in the scalp, but more follicular with more pustulation.

Trunk – Interscapular and presternal areas show small brown follicular papules covered by a greasy scales, extension and coalescence of which give rise to circinate patterns (petaloid form).

Flexures – Diffuse, well-marginated erythema with greasy scaling and a fissure covered with crusts. Secondary bacterial and candidial infection is common.

Seborrhoeic dermatitis can be associated with AIDS. Lesions may appear before other manifestations of AIDS.

Management

1. Agents for eliminating seborrhoeic dermatitis and dandruff. (a) Ketoconazole 2% shampoo or cream twice weekly for 2–4 weeks. (b) Shampoo containing 0.1% triamcinolone daily for 2 weeks. (c) Selenium sulphide shampoo 2.5% two or three times weekly. (d) Preparation containing 1–2% Zinc pyrithione. (e) Bifonazole 1% shampoo for scalp in infants and children. (f) Chloroxine shampoo. (g) Any non-medicinal shampoo containing surfactants and detergents will remove scales. They can be used every 2 days to control dandruff.
2. For extensive or inflammatory lesions – Application of corticosteroid (Betamethasone) lotion, or sodium sulfacetamide 10% lotion bd. Topical steroid mousse formulations (betamethasone valerate and clobetasol) are useful adjuncts for scalp seborrhoeic dermatitis because the foam melts at skin temperature leaving minimal residue.

For thick scalps – Overnight applications of a keratolytic agents, e.g. salicylic acid with or without plastic cap occlusion.

Malassezia folliculitis is an itchy follicular eruption on the back and shoulders which may resemble acne.

Oral therapy – Fluconazole 400 mg, Ketoconazole 200 mg od for 7–10 days, but the drug should be reserved for cases not responding to topical therapy because of the risk of hepatotoxicity.

CANDIDOSIS

Superficial Candidiasis

Superficial candida infections are usually caused by candida albicans. This organism is a common commensal in the mouth, vagina and GI tract in healthy individuals.
Secondary bacterial infection may occur.

Predisposing factors – Excessive sweating, maceration, obesity, diabetes, leukaemia, systemic antibiotics, immuno-suppression due to drugs, HIV, systemic steroids, pregnancy, oral contraceptives, and prolonged topical steroids, etc.
Occupational, e.g. housemaids (affection of finger web and toe webs).

Description – Moist erythematous patches at opposing surfaces of body folds.

There is scaling at the periphery of relatively drier patches. The patch may be surrounded with satellite lesions. In advanced cases, the surface of these patches may be eroded or even ulcerated with discharge of serous or seropurulent fluid.

Distribution – Groin, beneath pendulous breasts, axillae and abdominal folds, neck folds and natal cleft in obese.

Tr. – Application of clotrimazole or miconazole as cream or lotion. Topical antibacterial if secondary infection. Drying of affected parts after washing and powdering the parts with clotrimazole or miconazole powder.

Cutaneous Candidiasis

1. ***Onychia and paronychia*** – Inflammation of the posterior nail fold, edges of the nails are eroded and the nail discoloured. Seen mostly in housewives, domestic and dish washers.
2. ***Intertriginous candidiasis*** – as described above
3. ***Candida in nonintertriginous areas*** – appear usually as satellite lesions of mucosal or intertriginous infection as erythematous, slightly raised 1–2 mm papules with superficial collarette of scales.
4. ***Erosio interdigitalis*** – Maceration and erosion in the webs of the fingers, and toes.

Mucosal Candidiasis

1. ***Oral thrush*** – (Acute pseudomembranous candidiasis) is characterized by a sharply defined patch of creamy white pseudo- membrane which when removed leaves an underlying erythematous base. One or more patches may occur. Tissues involved are the tongue, gums and palate. Rarely erosions and ulcerations may occur in the pharynx and oesophagus. Diseases such as diabetes, malignancy and immunodeficiency states, antibiotic therapy and dentures may predispose, and it may be occasionally the primary presentation in AIDS.
   Tr. – Clotrimazole % as mouth paint. Fluconazole 50–100 mg/day for one week or 150 mg/day for 3 weeks in immunocompromised or debilitated patients.
2. ***Perleche*** – is fissuring and maceration at the angles of the mouth.
3. ***Vulvo-vaginitis*** – often associated with itchy and creamy white vaginal discharge.
4. ***Balanoposthitis*** – (balanitis). Two forms are associated with *Candida spp.* Both types may be acquired sexually.
   A true superficial but invasive infection occurs particularly in diabetic and uncircumscribed males. It is characterized by intense pruritus, discomfort, erythema and swelling that is localized primarily to the glands, but may extend to involve the penile shaft and scrotum. Treatment comprises topical antimycotics and systemic azoles.
5. ***Chronic mucocutaneous candidiasis*** is characterized by recurrent and persistent infection of skin, nails and mucus membrane without disseminated candidiasis.

Management

The predisposing cause must be investigated and treated. Wet work must be avoided in paronychia. Intertriginous areas must be kept dry. Obese patients must reduce weight.

Imidazole derivatives – clotrimazole, miconazole or econazole topically for 2 to 3 months on nails, 1 month on skin.

Ketoconazole tablets: 200 mg daily for initial 10 days in severe cases.

Vulvo-vaginitis may require clotrimazole vaginal tablets in addition for 8 to 15 days.

Antifungal powder clotrimazole or miconazole in affected axillae, intertriginous areas, i.e. below breasts, abdominal fold, groins, between toes.

DEEP FUNGAL INFECTIONS

Mycetoma

(Madura foot) is a chronic subcutaneous infection caused by either actinomycetes or filamentous bacteria (actinomycetomas), or fungi (eumycetomas), with a tendency to form large colonies in tissues. These are discharged as granular matter (grains) through sinuses (Fig. 17).

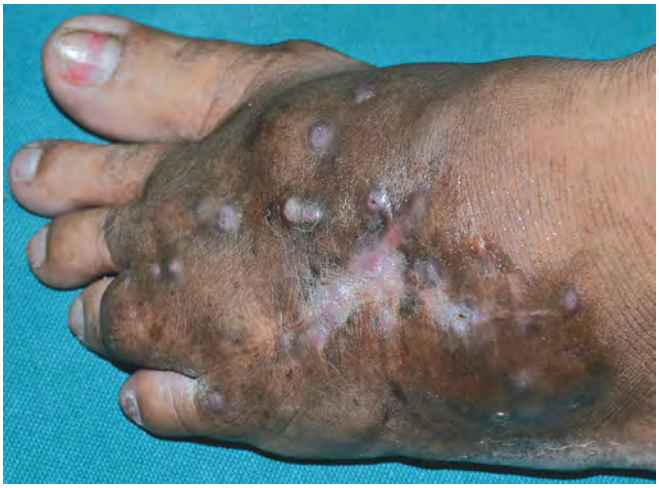


Fig. 17: Foot mycetoma

Description – The lesions start insidiously, with a hard subcutaneous swelling which enlarges and discharges pus through small sinuses which discharge dark (eumycetoma) or pale coloured (actinomycetomas) granules. Characteristically, small fungal or actinomycete aggregates (grains) are present. Lytic bone lesions and periosteal proliferation may develop.

Sites – The foot is most frequently affected being exposed to injury. Rarely hand, shoulder or buttocks.

Diagnosis – Biopsy or removal of grains from sinuses; these can be examined by direct microscopy, histopathology and culture.

Treatment – Dapsone 20 mg daily for 6–24 months. Cotrimoxazole 2 tabs (480 mg) b.d. for 6–24 months. Inj. Streptomycin 1 gm im daily × 2 months. Inj. Amikacin 500 mg im daily for 3 weeks followed by 2 weeks of rest. To be repeated if required. Saturated solution of pot. iodide 5-30 drops t.d.s. can also be given. (a) Actinomycetoma – 9 months course of (i) Streptomycin + cotrimoxazole or dapsone (ii) Co-trimoxazole + streptomycin or (iii) Tetracycline + Strepto + Rifampicin (b) Eumycetoma – Ketoconazole or Itraconazole or Amphotericin B (in resistant cases).

Surgery – Deep debridement. Amputation as a last resort.

Sporotrichosis **–** Caused by Sporothrix schenckii. *Types* – (a) Lymphatic presents as a nodule which ulcerates. Later a chain of nodules are seen along lymph vessels draining the area. (b) Fixed – Single infiltrated plaque. *Tr.* – Itraconazole or saturated solution of potassium iodide.

Chromoblastomycosis **–** Painless warty papule enlarges gradually to form a cauliflower-like hypertrophic plaque, studded with black dots.

Subcutaneous phycomycosis **–** Slowly spreading subcutaneous swelling with smooth edge, but no ulceration. Common site are limbs, face. *Tr.* - Pot. iodide.

PYODERMA

Skin infections produced by pus forming organisms, mostly Gram positive group A beta haemolytic streptococci, and Staph. aureus. A variety of clinical pictures are produced depending on site of infection.

Clinical Manifestations

1. **Impetigo** – Impetigo is an acute superficial infection of the skin caused by Staph. aureus, or less commonly group A-hemolytic streptococci. It presents as golden yellow crusts, formed from exuding serum (Fig. 18), usually affecting the face. The lesions spread locally and may coalesce; multiple lesions are common. Blisters can be a feature and, as they rupture, typical crusts form at the edge of the lesions. Systemic upset is not usual.

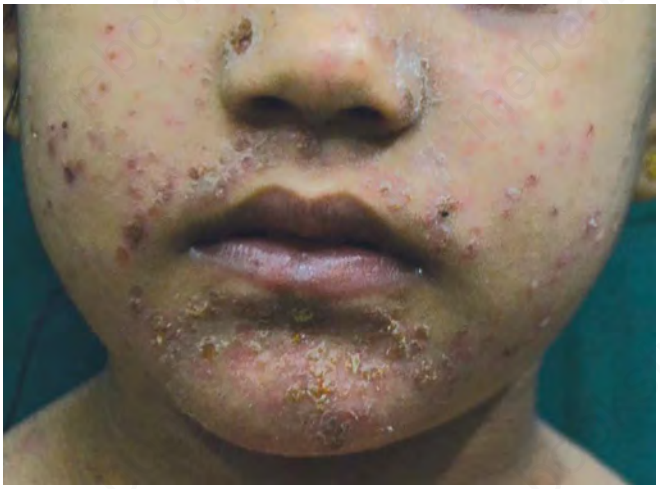


Fig. 18: Impetigo

   a. ***Impetigo contagiosa*** – The most superficial of all the pyodermas, it can occur as such, or secondary to scabies, pediculosis, insect bites, herpes, and eczemas. Common in children, it begins as an erythematous spot, rapidly forms a vesicle with clear fluid, which becomes purulent and dries forming a thick yellow crust. Removal of this crust, exposes underlying eroded surface with a little oozing, this fluid is contagious to the surrounding areas or infects the hair follicles giving rise to a folliculitis.

   b. ***Impetigo bullosa*** – Bullous lesions may be of limited extent but in very small infants, infections may spread widely causing fatal outcome without vigorous antibiotic therapy (Table 15).

   c. ***Impetigo circinata*** – Sometimes lesions of impetigo contagiosa appear grouped. With central clearing of older lesions and superficial crusting of peripheral lesions a circinate pattern appears. The lesions tend to be more localised.

2. **Ecthyma** – A deeper infection, usually seen in debilitated individuals or with poor hygiene. The lesions start as vesicles which dry up to form thick crusts, removal of which displays an underlying lake of pus in a saucer-shaped ulcer. It is found mostly on the legs, and heals with scarring.

Table 15: Differences between Impetigo contagiosa and Impetigo bullosa

	Impetigo contagiosa	*Impetigo bullosa*
Organism	Staph. aureus/Str. pyrogens	Staph. aureus
Age	Young children	Infants
Site	Orofacial, scalp, extremities	Face
Skin lesions	Thin walled blisters which easily rupture with formation of honey-coloured crusts. Lesions spread peripherally and coalesce	Fluid filled bulla rupture after few days to form thin varnish-like crusts Central healing of lesions with plaque formation
Complications	Glomerulonephritis Eczematization	Staphylococcal scalded skin syndrome

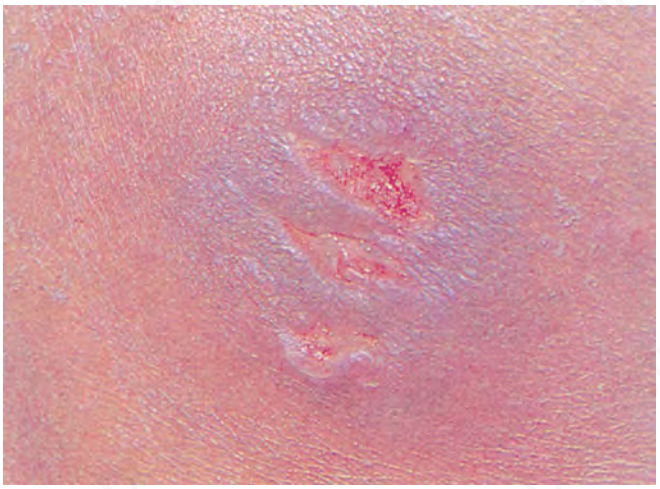


Fig. 19: Carbuncle

3. **Folliculitis** – A pyoderma of the hair follicle. These, are two types –
   a. *Superficial folliculitis (Bockhart's impetigo)* – Folliculitis of the superficial part of the hair follicles and perifollicular region giving rise to follicular pustules covered by crusts. Infection spreads from one follicle to another. This type of impetigo which appears on the legs becomes chronic till after some years atrophy of the skin results.
   b. *Deep folliculitis* – Sycosis barbae is a folliculitis of the beard area of the face. There is no pain but itching and burning may be the only symptoms, there is no oozing or weeping at any stage.
4. **Furuncle (common boil)** – is a deep-seated infection of the hair follicle around the hair root. The causative organism is most often Staphylococcus aureus. It is frequently found around the hairy areas of the body, especially those subjected to friction and maceration. Furuncles are painful. It starts as a firm nodule but softens and ruptures after a few days discharging pus. A thorough search for an underlying cause is mandatory in all cases of chronic recurrent pyodermas. Diabetes mellitus, poor general health, malnourishment, blood dyscrasias, chronic nephritis, immune deficiency should be ruled out.
5. **Periportitis –** Sweat gland abscesses, non-tender, rounded, fluctuant, erythematous nodules. Can occur in the scalp especially in children.
6. **Carbuncle** – is a conglomeration of boils. It is a deeper and more extensively infiltrated lesion. *Predisposing factor* – Uncontrolled diabetes mellitus. *Description* – It starts as a tender, erythematous, indurated deep plaque on the back, neck or thigh, associated with fever and malaise. Multiple pustules appear on the involved area which is now violaceous, and the mass breaks down at multiple points discharging pus. Often the whole area sloughs off leaving a deep ulcer.

   Site – Typically the nape of the neck (Fig. 19). Less often trunk and extremities.
7. **Hidradenitis suppurativa** is a chronic suppurative inflammatory disease of apocrine glands and surrounding tissues caused by *Staph. aureus* and *anaerobic streptococci.* It is most commonly seen in the axilla in females/and in perianal regions in males. Indolence and chronicity are the hallmarks of the disease.
8. **Cellulitis** – is an infection of the dermis and subcutaneous tissue usually caused by a group A streptococcus and Staph. aureus. It typically occurs near surgical wounds or a cutaneous ulcer or, like erysipelas, may develop in apparently normal skin. Recurrent episodes of cellulitis may occur with local anatomic abnormalities that compromise the venous or lymphatic circulation. In cellulitis the borders are indistinct.
9. **Erysipelas** – is an acute, inflammatory form of cellulitis that differs from other types of cellulitis in that lymphatic involvement (streaking) is prominent. Erysipelas is also more clearly demarcated from normal skin than cellulitis (Fig. 20). The lower legs, face and ears are most frequently involved. Fever, chills and regional lymphadenopathy are associated features. Recurrent erysipelas leads to chronic lymphoedema with elephantiasis.
10. **Intertrigo** – is inflammation of apposed skin surfaces. Predisposing factors are heat, moisture, friction and

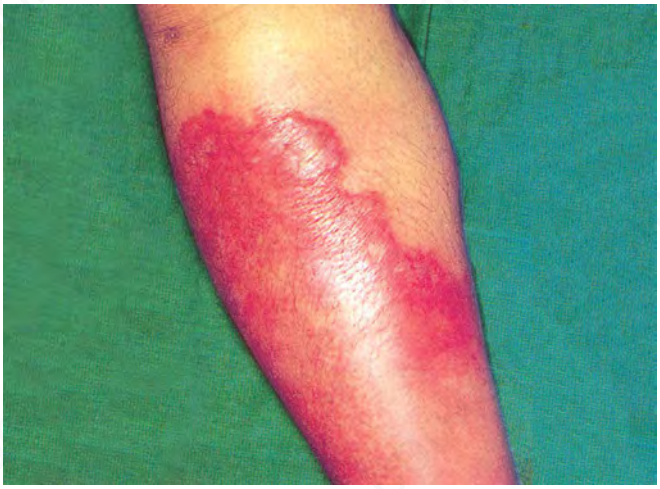


Fig. 20: Erysipelas

sweat retention; these cause maceration and inflammation in these areas. Chronic bacterial or candidial infection usually follows. Common organism is *Strep. pyogenes*. Initially the skin is red and somewhat macerated. The folds when separated reveal erythema of contiguous surfaces, covered by a macerated horny layer, usually with a deep fissure. In severe cases, there may be complete denudation of the surface. Itching, burning and exudation are usual. An offensive odour is due to coryneforms (Brevibacteria).

11. **Acute paronychia**
12. **Periportitis** (Multiple sweat gland abscesses) – Staphylo. infection which starts as multiple erythematous papules and nodules over face, forehead, scalp and upper trunk. These progress to form non-tender, thin-walled, fluctuant abscesses. There is no central follicular pointing as in the case of furunculosis.

Management

1. *Treatment of underlying cause* and attention to predisposing factors.
2. *Local hygiene.* Wash the parts with an antiseptic preferably Cetavlon lotion 0.5% or povidone iodide. Bandage, and change the dressing daily. Boil the clothes, bed linen and towels of the patient.
3. *Local treatment* – Wash the part well with soap and water, and remove the crusts. Apply an antiseptic lotion around the area consisting of 0.5 per cent cetrimide solution or povidone iodine. Furuncles if pointing should be incised, so also the blisters of impetigo. Apply Bacitracin, Fucidin, Neomycin, Mupirocin or povidone iodine skin cream or for chronic or recurring infections, use the povidone iodine solution 1 or 2 hours before bath on affected areas as well as over 4" to 6" of normal skin around.
4. *Systemic antibiotics* – for extensive and deep infections, especially if the pyoderma is chronic or situated on the upper lip, nose or cheek: Ampicillin 500 mg 6 to 8 hourly or erythromycin 500 mg, cephalexin 500 mg 6 to 8 hourly or co-trimoxazole.

Table 16: Viruses affecting skin or adjoining mucous surfaces

A. DNA viruses
1. Herpes virus group
Herpes simplex
Varicella zoster
2. Pox group
Molluscum contagiosum
Milker's nodules
Orf
Smallpox
3. Papovirus group
Human papilloma virus
B. RNA viruses
1. Coxsackie virus (hand, foot and mouth disease)
2. Retroviruses group
HIV virus

VIRAL SKIN INFECTIONS

See Table 16 for the viruses affecting skin or adjoining mucous surfaces.

Viral Warts (Verrucae)

Verrucae or warts are epidermal growths resulting from infection of the skin with a filtered DNA virus called the Human Papilloma Virus (HPV). They are autoinoculable and contagious. They can affect any part of the body. The type of wart is dependent on the anatomical site and age of the individual (Fig. 21).

Types

1. ***Verruca plana or juvenile warts*** – are seen in children usually on the back of the hands or on face. They are smooth, small, flat topped papules of skin colour.
2. ***Verruca vulgaris*** – These affect any part of the body especially the hands and feet, varying in size from pinhead to pea size. The surface is rough and hyperkeratotic. They are firm in consistency and not tender.

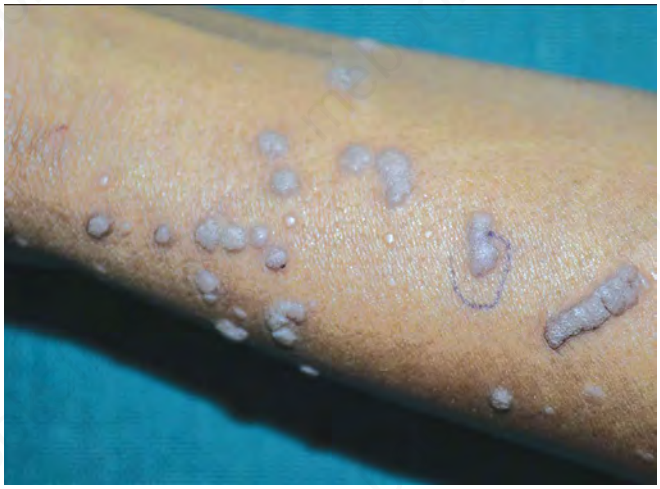


Fig. 21: Warts

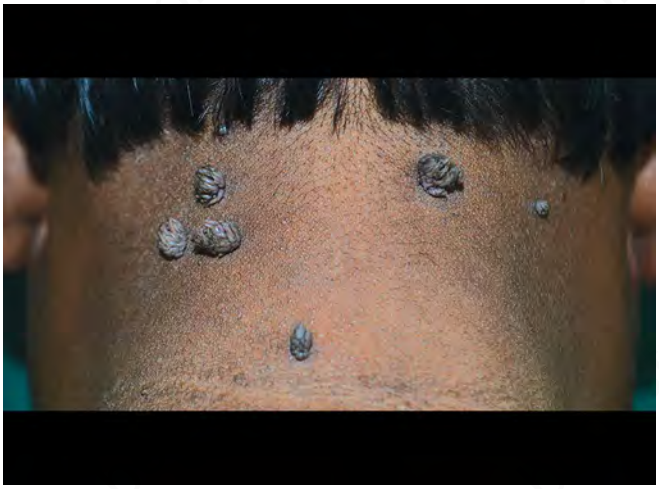


Fig. 22: Filiform warts

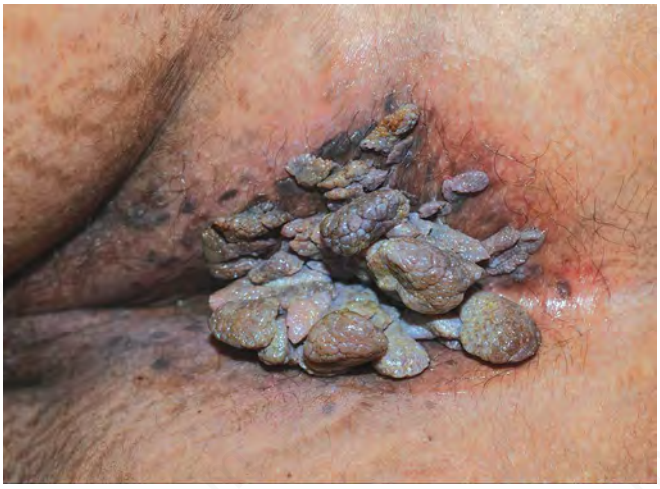


Fig. 23: Genital warts

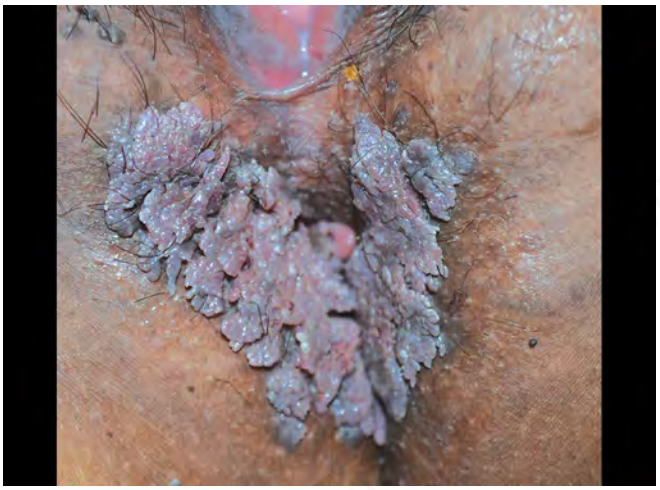


Fig. 24: Genital warts

3. ***Filiform warts*** – These are finger-like growths, slender and thin found on the face and neck (Fig. 22).
4. ***Plantar and palmar warts*** – These occur on the palms and soles of the feet. They are flat due to pressure, but are deep in the skin. They are painful and tender, occur on sites of pressure like the balls of feet and heels. Often a number of these warts conglomerate to form a mosaic wart. Clinically, it must be differentiated from a corn which also occurs on pressure points, tender at the centre, but has no papillomatous surface when scraped. The normal lines of the skin stop at the margins of a wart. When the surface is gently scraped, small bleeding points or black dots are seen.
5. ***Genital warts (Condylomata acuminata)*** –

   Predisposition – Sexually active adults of either sex.

   Description – Single or multiple (Figs. 23 and 24), white, pink, moist or slightly hyperpigmented hypertrophic warts which resembles a cauliflower. Early lesions may be flat.

   Distribution – Anogenital region – Penile, vaginal or rectal mucosa may be involved.

   Diagnosis – The verrucous, irregular surface of the lesion is highly suggestive. Biopsy may be necessary to exclude squamous cell carcinoma.

Occupational warts are common wart-like papillomatous and/or dome-shaped, deep warts with a smooth surface located on both dorsal and palmar sides of the hands. They occur in butchers and fish handlers.

Management: It is best to destroy the wart, by chemical, electrical or surgical means, the choice depending on the type and location of the wart –

a. *Chemical cautery* – With trichloracetic acid (50%), phenol (95%) or salicylic acid (30–40%) can be used in any of the warts. Genital warts can be more easily treated with local application of 25% suspension of podophyllum in tincture benzoin. First vaseline is applied on the skin surrounding the lesion to protect it from an overflow of the medicine. The podophyllum should be allowed to dry and after 2 hrs the whole area washed with soap and water. If the lesion is big, podophyllum may have to be repeated at weekly intervals. Sometimes the warts may disappear without any treatment.
b. *Cryotherapy* – With liquid nitrogen or carbon dioxide snow destroys the warts by freezing, and will leave no scar.
c. *Electrocauterization* – Under local anaesthesia.
d. *Laser surgery* – CO_2 laser therapy clears chronic, recalcitrant lesions, pulsed dye laser for vascular component.
e. *Keratolytic agents.* Salicylic acid (10–20%).
f. *Formalin* (2–3%) soaks in water for 15 minutes for plantar warts.

Molluscum Contagiosum

It is caused by a pox virus which gets implanted on the skin by contact with other infected individuals. The disease is common in children.

Description – Asymptomatic, multiple, small, skin-coloured or pink, dome-shaped papules (1 mm to 1.5 cm in diameter, with a central dimple or umbilication) (Fig. 25).
Distribution – Neck, axillae and upper chest more common.
Diagnosis – Examination of the keratotic debris reveals eosinophilic molluscum bodies.
Treatment – (a) Curettage of individual lesions. (b) Trichloracetic application. Application of KOH 10% or Tretinoin, cidofovir and imiquimod. (c) Cryosurgery. (i) Electrodessication.

Herpes Simplex

The DNA virus of herpes simplex causes a grouped vesicular eruption of the skin and mucous membranes. It manifests in two forms – (a) *Primary herpes simplex* occurs, when the patient has been exposed to the virus for the first time. (b) *Recurrent herpes simplex.* Following the infection, many patients become long-term carriers. There are

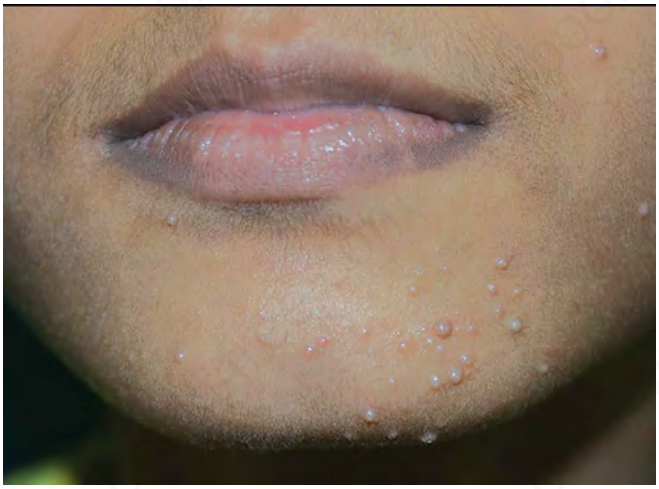


Fig. 25: Molluscum contagiosm

two strains of herpes simplex virus – (i) Type 1, i.e. (HSV-1) is primarily responsible for infection around the mouth, (ii) Type 2, i.e. (HSV-2) causes genital infection and is usually sexually transmitted.

Primary infections

A. ***Mucous membranes:***
   1. *Acute gingivostomatitis* – It is usually a primary infection, characterized by soreness of mouth, salivation, fever and malaise. There are vesicles in the mouth and submandibular gland enlargement.
   2. *Keratoconjunctivitis* – Presents with painful conjunctivitis, usually unilateral. Dendritic ulceration of the cornea may occur and lead to chronic scarring.
   3. *Genital herpes* – Usually acquired venereally with Type 2 strain in adults. In *females* there are grouped vesicles on the vulva, cervix or vagina. In *males* grouped vesicles on the glans or prepuce, or, less commonly, urethritis. Recurrent herpes on the penis is common in males (herpes progenitalis).

B. ***Skin:***
   1. *Disseminated herpes simplex* – Mostly seen in newborn infants. The brain, liver, lungs and other organs may be involved. It is often fatal.
   2. *Eczema herpeticum* – In patients of atopic dermatitis, herpes simplex sometimes develops into a severe varicelliform eruption.
   3. *Herpetic whitlow* – This is probably a true viral wound infection and manifests as an indolent inflammatory lesion, arising at the site of a minor

skin trauma, usually on a finger, in the form of deep, painful, grouped vesicles on the finger tip. *Facial lesions,* which may be multiple, can spread through rugby packs ('Serum pox') and among wrestlers. Axillary adenopathy and systemic symptoms occur. It occurs either in medical or paramedical personnel in whom HSV-1 is usually responsible.

4. *Anal infection* – especially in male homosexuals. Intense pain, tenesmus, blood-stained discharge and local vesicles are present.

Recurrent infections

1. *Herpes labialis* – Fever blisters and cold sores. A few hours before the onset, there is a feeling of burning, or pain; this is followed by a crop of vesicles which break down in 48 hours. These crops recur and the attack lasts for 3 to 7 days. It commonly occurs on the face at the mucocutaneous junction (Fig. 26). There may or may not be a scar left after the attack. It is precipitated by fever, strong sunlight, emotional stress, local trauma.
2. *Eye infections* – May recur as a superficial keratitis. More seriously uveitis.
3. *Genital infections* – Usually milder and shorter than the primary disease.

Recurrence of the latent virus, usually in the trigeminal ganglia, produces grouped vesicles on the face, usually on the lips (cold sores), attacks may be precipitated by sun exposure and concurrent illness.

Complications: (See Chapter on Infectious Diseases)

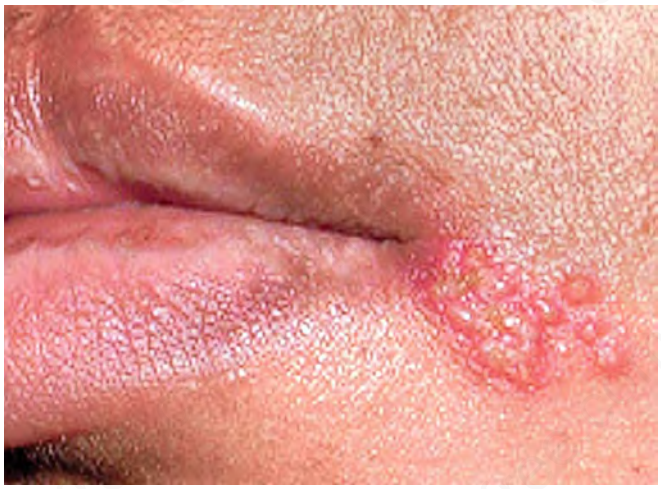


Fig. 26: Herpes labialis

Diagnosis – A swab taken from the base of the lesion is wiped across a glass slide for staining with immunofluorescent antibodies. The swab can also be placed in sterile saline for detection of viral DNA by PCR.

Management of skin lesions:

1. *Acyclovir (ACV)* – 5% cream applied every 4 hours. For severe infection ACV by mouth. Dose 200 mg 5 times a day (Children under 2, half the dose). IV acyclovir 5 mg/kg every 8 hours by slow infusion. If ACV is started early in an attack, i.e. during prodrome or on the first day, it significantly reduces duration and severity.
2. *Antibacterial therapy* – May be used in mucocutaneous herpes to reduce risk of secondary infection.

Herpes Zoster (Shingles)

A unilateral, inflammatory, vesicular eruption caused by a latent herpes varicella virus from within sensory ganglia which attacks the posterior root ganglion and produces the skin eruption secondarily along a dermatomal distribution.

Predisposing factors: Herpes zoster is more common in people with diminished cell mediated immunity. This includes elderly people, patients with lymphoma, those receiving chemotherapy or steroids, and individual with HIV. In contrast to herpes simplex, precise trigger for herpes zoster are not known.

Clinical Features

Incubation period – 7–21 days.

1. ***Pre-eruptive stage*** – Pain with hyperaesthesia along the course of the nerve, and fever.
2. ***Eruptive stage*** – May be the first manifestation of the disease in some cases.

Description – There are several oedematous patches along the course of a nerve with intervening clear areas, these are very tender and painful. A few hours later, they are surmounted with small vesicles in cluster (Fig. 27). The vesicles occur in crops. The contents may become purulent. The vesicles crust over, and in absence of secondary infection, clear within a week. Immunosuppression can result in atypical widespread lesions with the risk of systemic spread. Chronic ulcerative lesions may be seen in AIDS patients. The regional glands are painful and tender. An attack lasts for 2–3 weeks. The rash is usually unilateral. The rash leaves behind pigmentation and scarring.

Sites – The thoracic and lumbar dermatomes are most commonly affected. An eruption in the mandibular or maxillary distribution of trigeminal nerve is associated

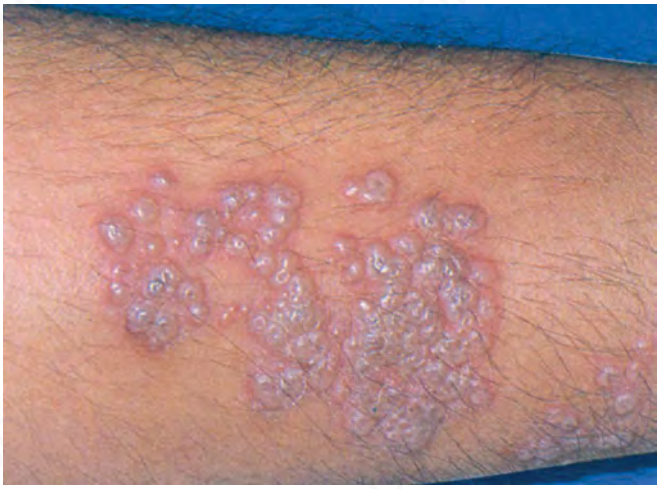


Fig. 27: Herpes zoster

with oral, palatal and pharyngeal lesions. If the ophthalmic division is affected, there may be keratitis or uveitis, with vesicles in the nose. In Ramsay-Hunt syndrome, the geniculate ganglion is affected. Pain in the ear and throat is followed by vesicles in and around the external auditory meatus associated with lower motor neuron facial paralysis.

Complications

1. *Post-herpetic neuralgia* – Risk factors – (a) Age > 50 years. (b) female sex. (c) Presence of a prodrome. (d) Severe or disseminated rash. (e) Severe pain at presentation. (f) Ophthalmic zoster. (g) PCR detectable varicella zoster viraemia.
2. *Keratitis and corneal ulceration* – when the trigeminal nerve is involved.
3. *Neurological* – including encephalitis, meningitis and myelitis.

Management

1. *Calamine lotion* applied several times a day.
2. *Analgesics.*
3. *Acyclovir* – 800 mg. 5 times a day p.o. will abort the attack if started within 48 hours.
4. *Antibiotics* – Systemically if there are signs of infection. Local application of an antibiotic ointment once the vesicles break down.
5. *Steroids* – given early reduce pain and incidence of complications including post-herpetic neuralgia in patients over 50 years of age. Prednisolone 40 mg daily for 6 days, reducing to zero over further 2 to 3 weeks.

Table 17: Aetiological factors for acne

• Androgens
• Follicular keratinization
• Heredity
• Propionibacterium acnes
• Immunological factors
• Environmental factors

6. *For post-herpetic neuralgia* – (a) Analgesics. (b) Amitriptyline. (c) Gabapentin. (d) Pregabalin. (e) Tramadol. (f) Carbamazepine.

Milker's nodule and Orf (Farmyard pox). Milker's nodule is a disease of Milker's or veterinarians caused by paravaccinia virus transmitted from udders of infected cows. The lesion is a single, erythematous nodule on a finger or not more than 4 on hands and forearm. They usually heal spontaneously.

9. ACNE AND OTHER FACIAL ERUPTIONS

Acne vulgaris is a disease in which the pilosebaceous follicle becomes oversensitive to normal levels of testosterone. Table 17 gives aetiological factors for acne.

Exacerbating factors – Acne worsens with stress and in premenstrual period. In patients with aggressive or recalcitrant acne, underlying cause may be a virilising syndrome in women, acromegaly, occupational exposure to acnegenic agents. Drugs that worsen acne are steroids, hormones (androgen and progesterone), anti-epileptic drugs, iodides; can follow facial massage.

Genetic and hormonal factors also play a role.

GRADING OF SEVERITY

- Mild disease: Open (black heads) and closed (white heads) comedones with sparse inflammatory lesions (Fig. 28). Some comedones are deep seated (submarine comedones).

Moderate: Numerous papules and pustules

Severe: Polymorphic eruption with comedones, papules, pustules, nodules and cysts.

MANAGEMENT

1. Topical therapies are the mainstay of treatment for mild acne.
   - ***Benzoyl peroxide*** 5% has antibacterial and keratolytic properties. It treats both inflamed and non-

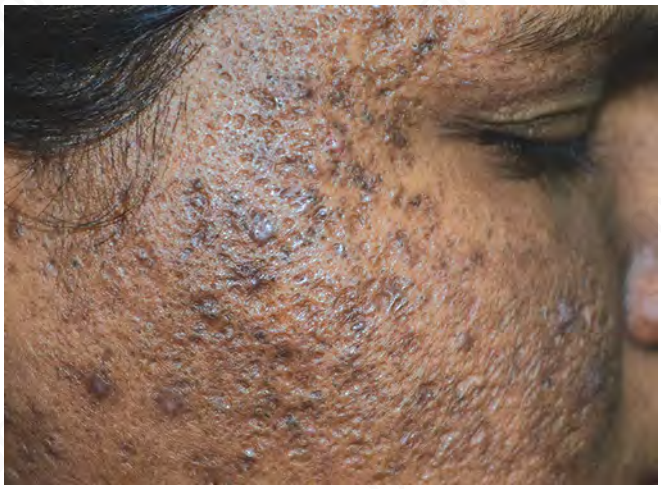


Fig. 28: Acne vulgaris with acne scars

inflamed lesions effectively, but can cause irritation and bleaching. Bacterial resistance is reduced when used in combination with antibiotics.

- ***Topical antibiotics*** are useful in reducing inflammatory lesions. Patients with greasy skin may tolerate clindamycin 1% and erythromycin 2% because of the alcoholic base. Clindamycin lotion is less irritating to dry, scaly skin.
- ***Topical retinoids*** are particularly useful in non-inflamed lesions. Tretinoin – normalizes follicular keratinization of the barrier layer and potentiates the penetration of other topical agents. Tretinoin cream or gel (0.25–1%), adelphane (0.1%) cream or gel or solution applied at night to entire face (cream for dry skin and gel for oily skin) and leave it for 20–30 minutes and then washed off with a mild soap. Isotretinoin (0.5–1 mg/kg/day) for severe nodulocystic acne resistant to therapy for 6 months (Total dose 100–120 mg). The drug is teratogenic and fertile women must use contraception while taking the drug and 4 weeks post treatment.
- Sulphur and resorcinol, e.g. sulphur calamine lotion.
- Salicylic acid can be used as an adjunctive therapy and is found in cleaners, toners
- Azelaic acid (20%) cream possesses antimicrobial, anti-inflammatory and comedolytic properties.

2. **Systemic therapy** antibiotics reduce inflammatory mediators and have to be used for 3–6 months. Higher doses may be required in patients with marked seborrhoea. Tetracycline 500 mg bd or doxycycline 100 mg bd for 2 weeks to 10 months. Erythromycin 500 mg bd if patient cannot tolerate tetracycline because of side effects or in pregnant women. Pulse therapy with azithromycin and clindamycin.
   - ***Corticosteroid*** – Prednisolone or dexamethasone once at night useful in females with severe acne unresponsive to conventional therapy.
   - ***Other drugs*** – Oral contraceptives, spironolactone, cyproterone acetate, flutamide and gonadotropin releasing hormone may help in young women after failure of conventional therapy.
   - ***Adjunctive therapy*** – Intralesional steroids for neurocystic lesions. Comedone extraction, chemical peels, dermabrasion, laser and light therapy.

Hormonal therapy is useful because androgen hormones mediate sebum production. Cyproterone acetate 2 mg with ethinyloestradiol 35 μg is effective if given for 3–6 months.

Management of scarring – (a) *Punch excision, elevation:* In depressed scars, punch elevation followed by full-thickness graft of normal skin. For superficial ice-pick scars punch elevation to raise level flush with surrounding skin. (b) *Intralesional triamcinolone and*/or *cryotherapy* for hypertrophic and keloid scars. (c) *Dermabrasion* – The skin is planed using a deep-wire brush. (d) *Laser therapy* – CO_2 ultrapulse and Er: YAG lasers have been used successfully.

VARIANTS OF ACNE

Acne fulminans is a rare disorder that can appear suddenly in the context of normal acne. There is a profound acne flare with muscular pain and fever. Osteolytic bone lesions have been described.

Treatment – High dose corticosteroids (1 mg/kg/day), followed by cautious introduction, after 2–3 weeks, of isotretinoin, 0.1–0.2 mg/d/p.o.

Infantile acne – Inflammatory lesions occur before or at about 3 months of age. Lesions are usually mild and disappear without scarring. Infantile acne often occurs in the context of a strong family history. Prepubertal resurgence of acne is likely.

Treatment – Topical therapies with or without oral erythromycin or trimethoprim. In severe cases, low dose isotretinoin may be required.

Pyoderma faciale is more common in young women in context of emotional stress and not necessarily with coexisting acne.

Treatment – Prednisolone 1 mg/kg/day and daily application of class IV corticosteroid for one week, followed by Isotretinoin 0.5 mg/kg/day gradually increased to 1 mg/kg/day for 4–6 months.

Acne conglobata – Multiporous comedones with intercommunicating abscesses, cysts and sinuses with serosanguinous fluid or pus.

Occupational acne – From exposure to industrial chemicals. Sites of involvement forearms, legs and retroauricalar region.

Cosmetic acne – Comedones on the chin.

Drug-induced acne – Comedone and papules on back of trunk and face due to androgens, steroids, oral contraceptives, anticonvulsants.

ACNE-LIKE ERUPTIONS

Acne rosacea is a chronic dermatosis that usually affects the face (Fig. 29). The hallmark is intermittent flushing of the face, which may occur spontaneously or may be triggered by hot and spicy food, alcohol, temperature changes, wind or emotional upset. It presents with papules and pustules and is often associated with telangiectasis. There may be associated conjunctivitis, keratitis and blepharitis. Rhinophyma is caused by hypertrophy of sebaceous glands leaving a red bullous nose. Fixed facial oedema may occur.

Periorbital and perioral areas are not affected.

Complications – (i) Ophthalmic – Blepharitis, conjunctivitis, keratitis. (ii) Rhinophyma. (iii) Lymphoedema – Forehead and infraorbital.

Treatment – 1. Sunscreens for patients with marked photosensitivity. 2. Topical agents - (i) Metronidazole (0.75%) for mild to moderate rosacea. Good response to papulopustular lesions. (ii) Retinoic acid (0.025%). 3. Immunomodulators – Tacrolimus 0.03% ointment, pimecrolimus 1% cream useful to wean off patients from topical steroids.

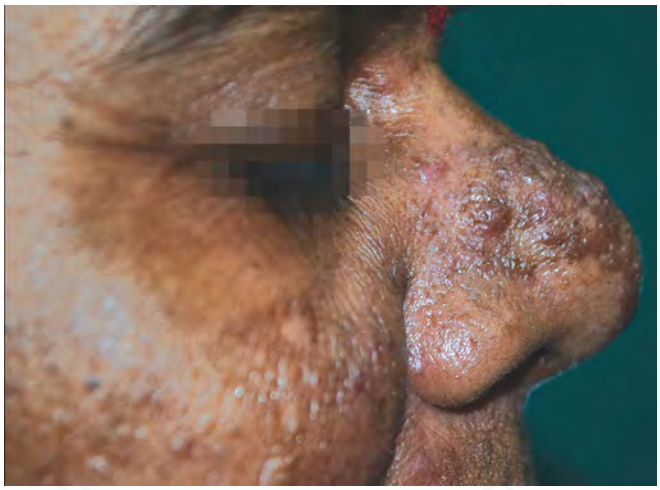


Fig. 29: Acne rosacea

Isotretinoin - Effective against all severities and all lesions. Dose - 0.5–1 mg/kg body weight daily for 6 months. 4. Antibiotics – Doxycycline – Initial 100 mg/d, then on alternate days for 3–6 months is the drug of choice.

Milia are small, subepidermal keratin cysts most commonly seen around the eyes resembling whiteheads. The eccentrically placed punctum seen in whiteheads is not visible in milia.

Sycosis barbae is caused by ingrowing curly facial hairs which penetrate the follicles.

Peri-oral dermatitis often occurs in women aged 20-35 years. It presents as red papules, which form superficial plaques around the peri-oral area, nasolabial folds and/or lower eyelids. It is minimally itchy. Cause is unknown.

Gram-negative folliculitis is a sudden eruption of pustular lesions often seen in those on long-term antibiotics and is commonly mistaken for a flare of acne.

10. DERMATITIS/ECZEMA

CLASSIFICATION

Table 18 gives the classification of eczema.

ATOPIC DERMATITIS

Atopic dermatitis (atopic eczema) is a common endogenous form of dermatitis and usually begins in childhood. It is an itchy, chronic and relapsing dermatitis.

Pathogenesis. Atopic dermatitis depends on a complex interaction between genes and environment. Genetic studies have shown linkage in three loci, but the environment in early life also has a profound influence on the immune over-activity that develops in this condition. An 'imbalance' in the immune system with preferential

Table 18: Classification of eczema

Endogenous eczema	*Exogenous eczema*
Atopic dermatitis	Contact dermatitis
Seborrhoeic dermatitis	Irritant
Nummular eczema	Allergic
Lichen simplex chronicus	Photodermatitis (Fig. 30)
Pityriasis alba	Infective dermatitis
Pompholyx	
Stasis dermatitis	
Asteatotic eczema	
Prurigo nodularis	

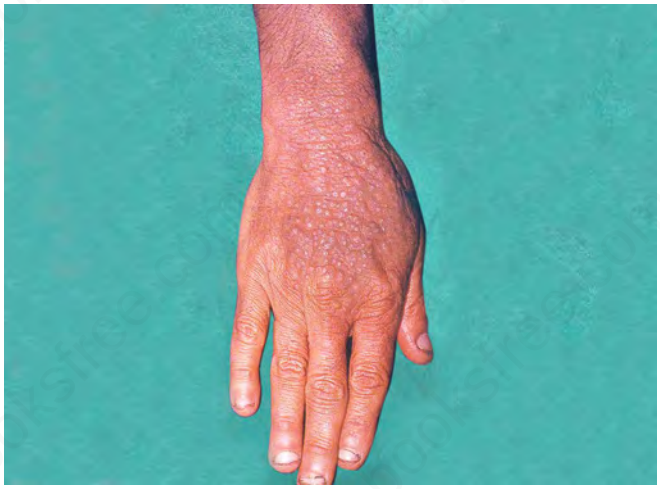


Fig. 30: Photodermatitis of hand

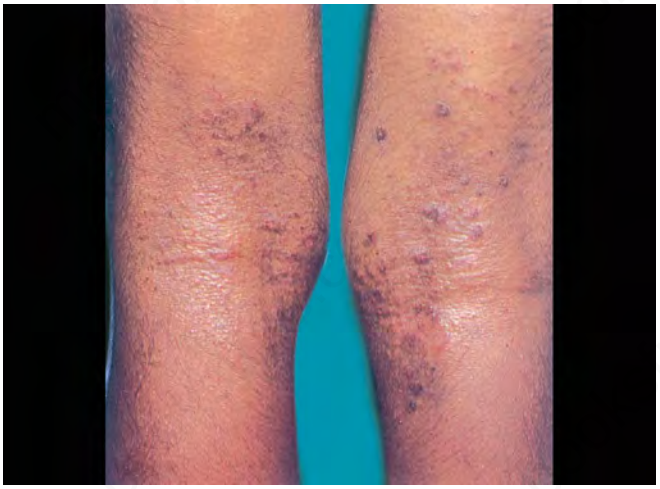


Fig. 31: Adult atopic dermatitis

activation of Th2 CD4 lymphocytes seems to be a crucial step in the development of atopy.

DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

- An itchy skin condition (or parenteral report of scratching or rubbing in a child) plus three or more of the following:
- Onset in infancy
- History of skin creases involvement (including cheeks) in children under 10 years
- History of generally dry skin in the past year.
- Other atopic features (or history of any atopic disease in a first-degree relative in children under 4 years)
- Visible flexural dermatitis (or dermatitis of cheeks/forehead and outer limbs in children under 4 years).

CLINICAL APPEARANCES OF ATOPIC DERMATITIS

- Acute dermatitis — Red, wet, weepy vesicles
- Subacute dermatitis — Red, dry, scaly
- Chronic dermatitis — Dry, thickened excoriated

In many patients, these clinical features overlap.

Distribution – In infants eczematous lesions are often present on exposed areas such as the cheeks, or outer aspects of forearms. In older child, eczema usually affects flexural sites such as the front of the elbows and popliteal fossa (Fig. 31), the front of the ankles and around the neck and face.

Variants

- Follicular eczema may occur, especially in dark skin.
- Discoid eczema is a morphologically variant seen in all racial groups. It can occur in both atopic and non-atopic individuals. It presents as itchy, well-circumscribed, crusted lesions, often on the limbs. Secondary infection is common.

INFECTIVE COMPLICATIONS OF ATOPIC DERMATITIS

Bacterial infection because bacteria adhere well to scaly, inflamed skin. It is usually not associated with pyrexia and malaise.

Eczema herpeticum describes a widespread herpes simplex virus infection of atopic skin with swinging pyrexia, malaise and occasionally severe morbidity. It presents with clusters of vesicles particularly on face, but can occur anywhere. These erode rapidly, leaving the typical picture of multiple, superficial punched-out or crusted lesions.

Investigations – These may reveal peripheral eosinophilia, raised serum IgE to a variety of common environmental agents (detected by radioallergosorbent tests or skin-prick tests). However, they are not needed routinely for diagnosis.

MANAGEMENT

1. ***Avoiding irritants and allergens.*** Use of cotton clothes and bedding covers. Families should be advised not to keep cats or dogs. Swimming can worsen dermatitis because of irritant effect of chlorine.

2. ***Dietary manipulation.*** Standard dermatitis therapies usually control the dermatitis without the need for dietary change.
3. ***Emollients and washing.*** Regular bathing to remove skin debris and crusts. Soaps should be avoided; bath oil and soap substitutes such as aqueous cream prevent the skin drying out.
4. ***Corticosteroids*** on inflamed skin only. Mild corticosteroids on face and under the nappy, and moderate strength on body. However prolonged use of topical corticosteroids, particularly if potent, is associated with many side effects.
5. ***Non-steroidal topical therapies*** – Tacrolimus, pimecrolimus and cyclosporine are immunosuppressants derived from the naturally acting macrolactam ascomycin. Unlike cyclosporine, tacrolimus and pimecrolimus are relatively small molecules that can penetrate through the skin and are therefore suitable as topical therapies. These drugs inhibitor production of the pro-inflammatory cyclin interleukin-2 (IL-2), reduce lymphocyte proliferation and activation, down-regulate high-affinity IgE receptor expression on Langerhans' cells, and reduce IgE-induced mediator release from mast cells and basophils.

   Dosage – Tacrolimus ointment 0.03% for patients aged 2 years and more, and 0.1% for those aged 16 years and more. Treatment is recommended for use b.d. for 3 weeks and then o.d. until improvement. Pimecrolimus cream 1% b.d. in patients aged 2 years and more with mild-to-moderate atopic eczema.

   The potency of tacrolimus is similar to that of 0.1% hydrocortisone butyrate and 0.1% betamethasone valerate. Patient's skin should be properly hydrated.

   Adverse-effects – Most common is a transient, mild burning sensation at the site of application.
6. ***Adjunct therapies***
   a. *Antibiotics* – for infected dermatitis. Oral broad spectrum antibiotics. Recurrent infections may be treated with antiseptic bath oil and emollients. For eczema herpeticum oral acyclovir can be given iv. if child is unwell.
   b. *Antihistamine* do not help because the itch of eczema is not histamine-mediated.
7. ***Systemic therapies*** are used because atopic dermatitis can prevent sleep, disrupt social and educational development and cause growth retardation.
   a. *Ultraviolet phototherapy* – Broad-band UVB, narrow-band UVA can be helpful, but their use in white-skinned patients is limited by the risk of skin cancer.
   b. *Immunosuppressants* – Cyclosporine, oral corticosteroids and azathioprine may be used in exceptional circumstances. Oral corticosteroids can be used for quickly controlling a severe flare of dermatitis. Initial dose 0.5–1 mg/kg/day, reduced every 3–4 days so that the course lasts 3–4 weeks. As the dose is reduced topical therapies must be intensified.
8. ***Complementary therapies*** – *Psychotherapy, hypnotherapy and acupuncture* can help patients relax, and may assist in breaking the itch-scratch cycle in some.

Lichen simplex chronicus results from persistent scratching and rubbing usually in adults of both sexes of a site of the skin. The causative pruritic lesions can be a transient mechanical or chemical irritation or at times an allergic contact dermatitis or atopy. Occasionally it may be habitual (circumscribed neurodermatitis). Whatever the etiological factor, the scratch-itch-cycle perpetuates the condition.

Description. Well marked hyperpigmented plaques and prominent crisscross skin markings so that the surface resembles tree-bark or leather. The skin becomes thickened and from persistent scratching tiny crusts or erosions may be observed.

Distribution. Body areas which can be easily scratched such as nape of neck, dorsa of feet, wrists, extensor surface of forearms, scalp and external ear canal.

Treatment – (a) Patient explanation of this habit. (b) Topical potent corticosteroids and occlusion of the area for 6–8 hours with a plastic film to enhance the effect. (c) Antihistamines for pruritus.

INFANTILE ECZEMA/DERMATITIS

Infantile atopic dermatitis Rash starts on the cheeks but may occur on any part of the body. Generally the nappy area is spared. Initial lesions are oedematous, erythematous papules which may become confluent. They are often markedly excoriated with exudation and crusting. When the dermatitis flares, intermittent morbilliform erythema may appear on the trunk. Secondary infection and lymphadenopathy often occur.

OTHER PATTERNS OF ECZEMA

Infantile seborrhoeic dermatitis – In young babies, it is often difficult to differentiate it from atopic dermatitis. Involvement of axillae in seborrhoeic dermatitis and the forearms and shins in atopic dermatitis are the best morphological discriminators (Table 19).

Pityriasis alba. Multiple mildly erythematous and scaly oval patches, which cause loss of pigmentation, seen on the face. Lesions can arise, infrequently, on non-facial skin. *Tr.* – Emollients, sunscreens on depigmented areas and 1% hydrocortisone ointment.

Table 19: Comparison of seborrhoeic and atopic dermatitis

	Seborrhoeic dermatitis	*Atopic dermatitis*
Age of onset	Less than 2 months	2–6 months
Pruritus	Uncommon	Common
Distribution of rash	Napkin area, axillae, scalp	Face, forearms, shins
Family history of atopy	30%	> 50%
IgE levels and RASTs to milk and eggs	Normal IgE, negative RASTSs	Elevated IgE, positive RASTs
Prognosis	Good, clears by 6 months	Chronic and relapsing, associated with asthma and hay fever

Lip-licking dermatitis – Chapped eczema around the mouth in a child with atopic dermatitis due to habits such as lip-licking, dribbling and thumb sucking, or as a result of chapping. It can become secondarily infected. *Tr.* – Emollients and occasionally 1% hydrocortisone ointment.

Juvenile plantar dermatosis presents in children as dry, shiny cracked dermatitis on plantar surface of big toe and forefoot. Some children are atopic or are involved in bare-footed sport. *Tr.* – Emollients, topical corticosteroids if severe flares.

Napkin dermatitis (Napkin rash) due to persistent irritation from urine or faeces due to lack of frequent changes of napkins. There is erythema and erosions of the buttock contours, and inner thighs sparing the inguinal flexures (unlike candidiasis). *Tr.* – Keeping the area dry and application of 1% hydrocortisone or soothing creams.
Stasis dermatitis is a type of eczema secondary to chronic venous insufficiency of the lower extremity.

Cl. Fs. – Onset is with oedema which after sometime is followed by irregular patches of pigmentation (due to deposition of hemosiderin), mostly above the ankle. Melanin may also be deposited in the skin as a result of scratching. Stasis can give rise to eczema and venous ulceration.

Stasis eczema may be of the chronic scaling type with itching and irritation. Other types of more diffuse dermatitis may occur. Occasionally there may be an id eruption on other parts of the body.

Nummular (Discoid) eczema presents as multiple coin shaped eczematous plaque lesions, bilateral but asymmetrically distributed on the extremities. *Tr.* – Mid to high potency steroids. Tacrolimus and pimecrolimus and tar preparations are also effective.

Pompholyx. Deep-seated vesiculation bilaterally symmetrical on palms and sides of fingers, also at times soles of the feet. *Tr.* – High potency topical steroid. For chronic and recurrent cases systemic prednisolone, cyclosporine, methotrexate.

Table 20: Causes of contact dermatitis

External agents causing contact dermatitis
• Degreasing agents
• Detergents
• Solvents
• Metal-working fluids
• Dusts and friction
• Low humidity
• Allergenic chemicals
• Rubber and plastics
Common allergens causing contact dermatitis
• Nickel
• Fragrance
• Rubber
• Medications including topical corticosteroids, lanolin, neomycin
• Chromate
• Formaldehyde and other biocides
• Epoxy resin
• Plant allergens
• Hair-dressing chemicals
• Direct or airborne contact may occur
• Cosmetics

Asteatotic eczema. Skin of trunk and limbs becomes erythematous, dry and pruritic and shows a crazy-pavement type of fissuring. It occurs due to excessive drying during winter months and in the aged. *Tr.* – Topical steroids and ointment and application of emollients.

Prurigo nodularis. Severe itching disorder in which rubbing and scratching of a skin area leads to formation of hemispherical nodules with warty surface over lower or upper limbs. *Tr.* – Intralesional inj. triamcinolone 10 mg/ml, or high potency topical steroids under occlusion. Antihistamines.

CONTACT DERMATITIS

Contact dermatitis is an eczematous eruption caused by external agents (Table 20).

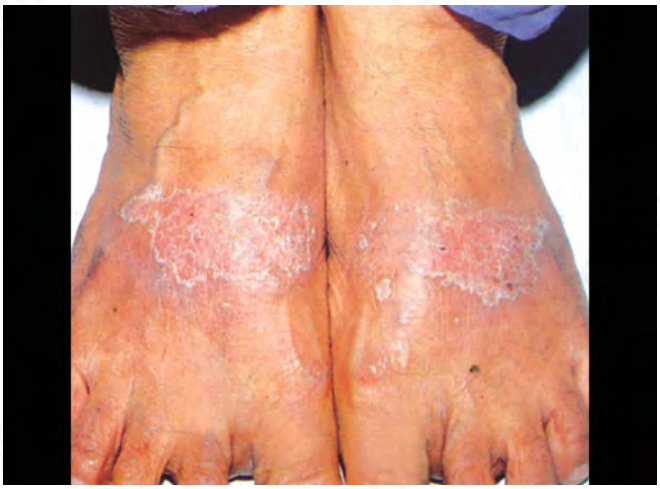


Fig. 32: Contact dermatitis due to footwear

Causes can be broadly divided into irritant substances that have a direct effect on the skin, and allergic chemicals with which dermatitis follows delayed type IV cell-mediated hypersensitivity reactions. Contact dermatitis often exacerbates pre-existing endogenous eczema.

Irritant contact dermatitis. Any physical or chemical agent that is capable of producing, if applied for sufficient time and in sufficient concentration can lead to irritant dermatitis. Dermatitis occurs when the repair capacity of the skin is exhausted or when the penetration of chemicals excites an inflammatory response. It is often occupational in origin, the most common industries are those in which workers engage in wet-work (e.g. hair dressing, cleaning, metal engineering, food processing, fishing). Pre-existing dermatitis (particularly of the hands) of an atopic nature is a strong risk factor for developing irritant contact dermatitis (Fig. 32).

Corticosteroid hypersensitivity. Hydrocortisone has the greatest sensitizing capacity, followed by budesonide.

DIAGNOSIS OF CONTACT DERMATITIS

- Sharp demarcation in the distribution of the dermatitis.
- Definite history
- Patch-testing – The allergens are applied on day 1, left on for 48 hours and then removed; readings are taken at 48 and 96 hours. Care must be taken to ensure that the allergens do not cause false-positive irritant reactions.

Table 21: Drugs that commonly cause rashes

• Antibiotics (penicillins and their derivatives like ampicillin, cephalosporins, sulphonamides and griseofulvin)
• Non-steroidal anti-inflammatory drugs
• Anticoagulants
• Allopurinol
• Gold
• AKT drugs

Management – (a) Elimination of causative factors. (b) Topical corticosteroids with emollients and soap substitutes when appropriate. (c) Immunosuppressant (cyclosporine, azathioprine) for very resistant cases.

Photodermatitis

Infectious eczematoid dermatitis is seen mainly around discharging wounds or ulcers and other moist skin lesions. Features are an area of advancing erythema, occasionally with microvesicles.

11. DRUG REACTIONS AND THE SKIN

A rash is usually the most obvious manifestation of hypersensitivity to a drug (Table 21).

Causes of cutaneous drug reactions. Immune-mediated hypersensitivity reactions are the most common cause of drug rashes.

Immunological drug reactions

Type I hypersensitivity reactions occur when a drug-protein conjugate cross-links two or more specific IgE molecules fixed to mast cells or basophils. *Clinical features* – Itch, urticarial rash, and less commonly bronchospasm, laryngeal oedema and anaphylaxis. Drugs commonly responsible are aspirin, opiates, penicillins and some vaccines.

Type II reactions involve binding of antibody to cells and with subsequent binding of complement and cell rupture. When this arises on the surface of platelets, it may produce thrombocytopenic purpura (e.g. quinidine).

Type III hypersensitivity reactions are mediated by intravascular immune complexes. These occur when drug antigen and antibodies, usually of IgG or IgM class, are both present in circulation, with the antigen present in excess. *Clinical features* – Fever, purpuric or urticarial rash, nephritis and focal inflammation of GI tract.

Type IV hypersensitivity reactions to topical medications produce an eczematous response at the site of application.

Drug responsible for delayed reactions include topical antibiotic neomycin, topical hydrocortisone, and sunscreens containing para-amino-benzoic acid.

Patterns of drug rashes

Exanthematous reactions **(**Toxic erythema) typically comprise symmetrical erythematous nodules and/or papules on trunk and limbs with sparing of the face. The rash fades with desquamation after stopping the drug. If the drug is continued, generalized exfoliative dermatitis may develop.

Purpuric drug eruptions due to bleeding into the skin. In severe cases, there may be urticarial lesions, hemorrhagica blisters and even cutaneous ulceration. Drugs implicated in cutaneous vasculitis include ampicillin, thiazide diuretics, frusemide, sulphonamides and hydralazine.

Simple purpura without vasculitis may be seen with any drug that affects platelet function or coagulation (e.g. aspirin, NSAIDs, heparin, warfarin).

Erythema nodosum is an erythematous nodular tender eruption 2–4 cm in diameter usually affecting external aspects of the legs, thighs and forearms. It is caused by antigen-antibody reaction and deposition of immune complexes in and around blood vessels. Erythema nodosum is associated with acute streptococcal infection, rheumatic fever, primary tuberculosis, acute sarcoidosis, sulphonamide drugs and pregnancy.

Erythroderma and exfoliative dermatitis. Extensive confluent erythema with subsequent desquamation is one of the most serious drug reactions in the skin. It may be preceded by exanthematic drug reactions or may arise *de novo.* Complications include hypothermia, fluid and electrolyte imbalance, and occasionally cardiac failure.

Urticaria and anaphylaxis. (See urticaria).

Lichenoid eruptions. Clinical and histological features resemble those of lichen planus. In contrast to lichen planus, oral involvement is rare. The eruption may start months after the causative drug was started. Hyperpigmentation and scaling are commonly seen as a part of the rash, and resolution is slow after the drug is withdrawn. Drugs include penicillamine, gold, β-blockers, thiazide diuretics, captopril, antimalarials and chlorpropamide.

Fixed drug eruption occurs at the same site(s) each time the offending drug is taken.

Causative agents – Tetracyclines, sulphonamides, phenolphthalein, oxyphenbutazone.

Description – The lesions, which are often painful and may cause a burning sensation, appear as clearly demarcated oval or round erythematous plaques which are sometimes bullous and usually 20 mm in diameter, though lesions up to 10 cm in diameter may occur (Figs. 33 and 34). After 1–2 days the lesion(s) become violaceous. Typically, there are one to three lesions. Lesions fade over 7–10 days and leave a hyperpigmented patch.

Sites – Usually the hands, feet, glans penis or lips. Lesions always occur at the same site.

Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Erythema multiforme is a condition characterized clinically by target-like (bull's eye) erythematous lesions, most pronounced on the trunk and palms and soles (Fig. 35). The mucous membrane may be affected, and severe cases

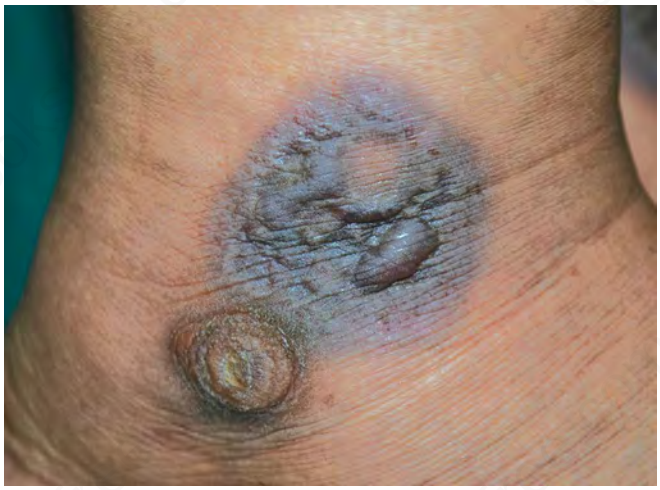


Fig. 33: Fixed drug eruption

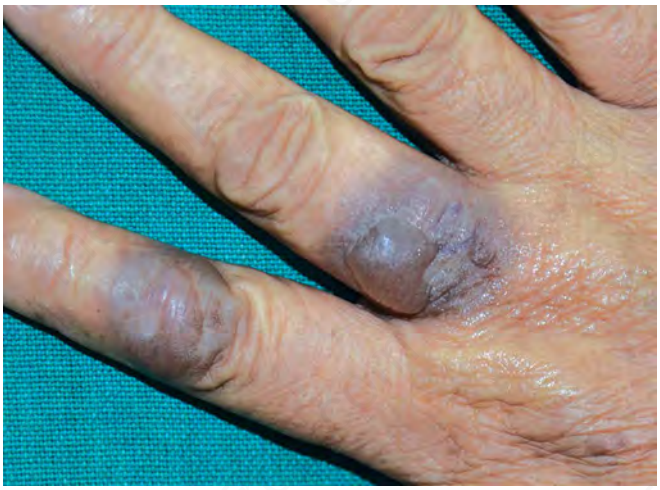


Fig. 34: Fixed drug eruption

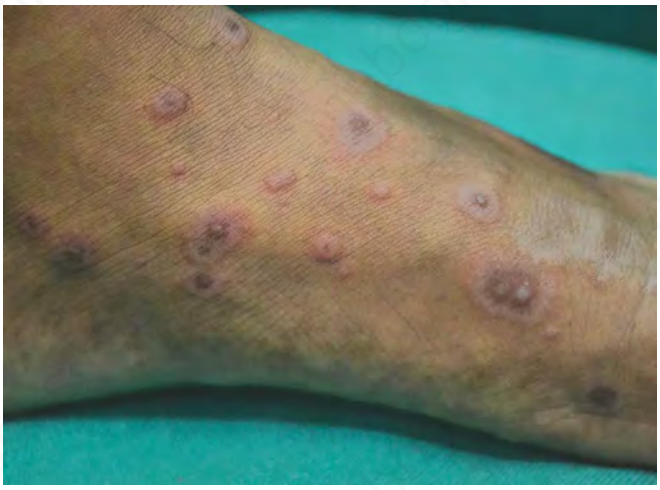


Fig. 35: Erythema multiforme showing target lesions

Fig. 36: Stevens-Johnson syndrome

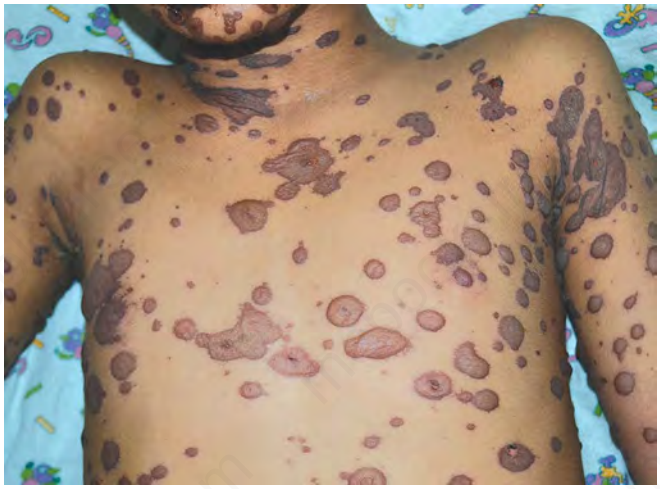


Fig. 37: Stevens-Johnson syndrome

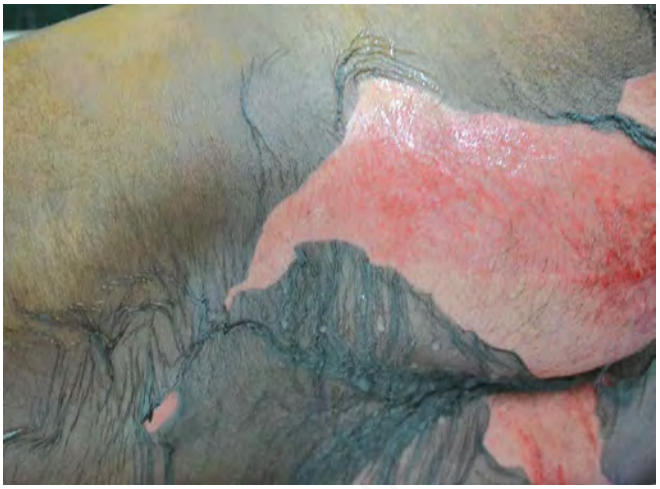


Fig. 38: Toxic epidermal necrolysis

patients develop fever, malaise, myalgia and arthralgia (Stevens-Johnson syndrome). Erythema multiforme is an immune complex mediated reaction to a variety of causes. In particular herpes simplex infection, drugs (especially sulphonamides) and mycoplasma. Other possible causes include AIDS, malignancy, other infections and connective tissue diseases.

Stevens Johnson syndrome (Figs. 36 and 37) is the severe form of erythema multiforme with conjunctival involvement and blistering and erosion of oral and genital mucosa. Usually there are widespread cutaneous blisters, but sometimes the mucosal features are associated with modest macular target lesions on the periphery.

Toxic epidermal necrolysis is preceded by a flu-like illness lasting 3–5 days, this is followed by fever, mucous membrane involvement and extensive erythematous skin lesions which either develop bullae or peel off in sheets, either spontaneously or when pressure is applied (Nikolsky's sign) (Fig. 38); mouth and eyes are often affected and manifest as hemorrhagic crusts, and white pseudomembrane of the lips.

Pneumonia complicates about 30% of cases as a result of sloughing of the epithelium lining the respiratory passages. Drugs responsible can be phenytoin, carbamazepine, sulphonamides, ampicillin and allopurinol. Causative drugs have been taken 1–3 weeks period preceding the eruption. There is occasionally a history of previous rash with the suspected drug. Mortality is 20–30%, and supportive treatment in ICU is needed in most cases.

Table 22: Differences between staphylococcal scalded skin syndrome and toxic epidermal necrolysis

	Staphylococcal scalded skin syndrome	*Toxic epidermal necrolysis*
Aetiology	Staph. aureus	Drugs, neoplasms, infections, graft-versus-host disease
Age	Infants and children	Adults
Constitutional disturbance	Mild	Severe
Course	1–2 weeks	More than 2 weeks
Scarring	Absent	May occur
Prognosis	Good	Bad
Treatment	Anti-staph. drugs	Stopping offending drugs

Staphylococcal scalded skin syndrome (SSSS) is caused by *S. aureus* and occurs mainly in infants and children. The onset is acute with fever and diffuse tender erythema followed by development of large fluid filled bullae which soon rupture. Site of lesions is periorifacial and body folds. Later the skin appears scalded, discoloured and denuded (Table 22).

12. PHOTOSENSITIVITY DISORDERS

Photosensitivity disorders involve abnormal sensitivity to ultraviolet (UBV and UBA) and sometimes visible sunlight. The clinical manifestations are diverse and include the exaggerated sunburn response, blistering and scarring, itchy, papular, eczematous or urticated eruptions and rarely, early onset of severe photodamage with skin cancer.

PATHOGENESIS

A specific wavelength interacts with a chemical component (chromophore), which undergoes excitation, causing clinical events mediated by toxic or allergic mechanisms.

1. **Exaggerated sunburn response** – is the most common manifestation of a sensitive response. UVR rays are responsible for most sun burns.

   Drug-induced photosensitivity – A phototoxic response is induced when ultraviolet light, and sometimes visible light, absorbed by the drug produces local damage to the skin and subsequent sunburn like erythema. Each drug has characteristic clinical features that are a function of the chemical properties of the drug and its anatomical location within the skin. Amiodarone causes photosensitivity in about 40% of patients, typically with burning erythema developing within 2 hours of sun exposure. Other drugs that may cause exaggerated sunburn response are thiazide diuretics, chlorpromazine, quinine, some forms of tetracycline and fluoroquinolone antibiotics.

   Other disorders in which sunburn-like erythema may be the presenting feature of photosensitivity:
   - Patients with xeroderma pigmentosum develop chronic cutaneous photodamage in early childhood, and subsequently skin cancers.
   - Erythropoietic porphyria is also associated with intolerance of sunlight since early childhood.
   - In Smith-Lemli-Opitz syndrome, sunburn-like erythema is observed on the first exposure to sunlight with redness within minutes that persists for 24 hours or more.

2. **Photosensitivity induced by topical agents**

   a. ***Phototoxicity.*** Here, injury results from interaction of the photosensitizing agent on the skin with ultraviolet or visible radiation, leading to release of reactive oxygen species and subsequently inflammatory mediators. Only brief exposure to sunlight can produce erythema, oedema and blistering.

   b. ***Photoallergy*** is a type IV delayed hypersensitive response. Important topically applied chemicals responsible are fragrances such as musk and 6-methylcoumarin, and sunscreens such as para-aminobenzoic acid and benzophenones. Photoallergy presents with worsening erythema associated with an eczematous rash a few days after sun exposure.

   Diagnosis can be confirmed by phototesting with the suspected allergen.

3. **Sun-induced blistering.** A relatively small dose of UVR or visible light may produce blistering in phototoxic drug reactions and in bullous porphyrias.

   Drugs. Some drugs produce blistering and skin fragility, features similar to those of bullous porphyrias, and the term 'pseudo-porphyrias, is used to describe this syndrome, in which porphyrin studies are normal. *Drugs responsible* – Naproxen, nalidixic acid, frusemide, tetracycline antibiotics, amiodarone and

isotretinoin. Newer fluoroquinolones produce a more acute pattern of hypersensitivity. Similar changes are seen in chronic renal failure, on sun exposure independent of medication.

Porphyria. Sun-induced blisters on the backs of the hands are seen in bullous porphyrias. Other features include skin fragility with erosions, hypertrichosis and skin pigmentation. The tense blisters heal slowly to produce atrophic scars, milia and hyperpigmentation.

4. **Eczema and eczema-like photosensitive eruptions.** Most common is seborrhoeic dermatitis. Atopic eczema may also be aggravated by exposure to sunlight. Diagnosis is confirmed by abnormal responses to formal light-testing.

ACQUIRED PHOTOSENSITIVITY SYNDROMES

1. ***Polymorphic light eruption*** is the most common syndrome. It is more common in females. Features are itchy, papular eruption on some sun-exposed sites which develops within a few hours of sun exposure and persists for up to 7 days. *Treatment* of acute attacks is with potent topical corticosteroid or a short course of systemic corticosteroids. In severe cases, desensitization therapy with UVB phototherapy or psoralen plus UVA therapy should be considered.
2. ***Other acquired photosensitivity syndromes*** are rare.
   - Hydroa vacciniforme occurs in childhood with crusted vesicles on the face following sun exposure that heal leaving depressed scars.
   - Actinic prurigo begins in childhood with an eczematous eruption that is more severe on sun-exposed sites and is associated with prurigo nodules caused by severe pruritus. It is often a chronic persistent disorder.
   - Solar urticaria is usually seen in adults, who present with sun-induced urticarial wheeling.

Harmful effects of solar radiation:

- Sunburn (acute effect)
- Photoaging: Potential long term effect of repeated sun exposure
- Keratoses, both melanoma and nonmelanoma skin cancers

Sunscreens – are agents that alter the effects of UV radiation on skin by absorption or reflection of a part of the incident radiation.

Indications for sunscreens – In most dermatological conditions requiring sunscreens (e.g. hyperpigmentation, photosensitivity disorders like polymorphous light eruptions or photocontact dermatitis) physical or broad spectrum screens are required. Physical sunscreens containing titanium dioxide or zinc oxide (or calamine) are less cosmetically acceptable since they tend to give pasty look to the skin. Chemical sun screens act as filters not allowing penetration of UV light to viable cells. Most common chemical compound used is para-amino benzoic acid (PABA).

Method of application – A sunscreen is to be applied generously on dry skin and all exposed areas of skin including the rims of the ears, lips, nose, back of neck and feet, 30 minutes before exposure. It requires to be reapplied every 2 hrs if sweating or swimming.

Adverse reaction to sunscreens – Stinging, burning, itching. Contact urticaria, irritant contact dermatitis (esp. PABA and its derivatives), acnegenicity (induce or exacerbate acne), and photosensitivity.

Types of sunscreens – (a) Physical: titanium dioxide, calamine. (b) Chemical: PABA, Methyl anthranilate octyl methoxycinnamate, avobenzone, oxybenzone, ethyl p-methoxycinnamate. Systemic photoprotection-useful drugs are beta-carotene, antimalarials and psoralens.

Sun-aggravated disorders. Common conditions include psoriasis, eczema, erythema multiforme and herpes simplex infections; rare are dermatomyositis and lupus erythematosus.

Patients with congenital or acquired metabolic deficiency may also show worsening rashes with sunlight. (a) In Hartnup disease, there is a dry, scaly rash on sun-exposed sites exacerbated by sunlight. (b) Also pellagrous rash. Pellagra may be encountered in chronic alcoholics or in those with GI or severe psychiatric disorders, or as a complication of therapy with isoniazid, 6-mercaptopurine or 5-fluorouracil.

SELF-LIMITING PAPULOSQUAMOUS DERMATOSES

Pityriasis rosea. Usually located on the trunk.
Aetiology **–** Probably viral, associated with human herpes virus (4HV, 6 and 7).

Cl. Fs. Healed patch followed by a secondary lesion of oval, annular erythematous plaques. These plaques show a ring of scale, attached to periphery of lesion and collarette. The lesions are arranged across the lines of the ribs (fir tree or Christmas tree appearance). When scratched across the long axis, the scales tend to fold across the line of scratch ('hanging curtain sign').

Tr. – Symptomatic treatment for itching.

Pityriasis rubra pilaris is a rare erythrosquamous dermatosis of unknown aetiology characterised by small papules with a central keratin plug, perifollicular erythema. There is a tendency to become confluent with an area of sparing, pityriasis capitis and palmoplantar keratoderma. The condition begins often with seborrhoeic rash on face and scalp which then spreads to trunk and limbs.
Tr. – Topical keratolytic agents, systemic steroids.

13. PAPULOSQUAMOUS ERUPTIONS

PSORIASIS

A chronic, recurrent, inflammatory disease of the skin of unknown origin, characterized by well-circumscribed erythematous, dry plaques of various sizes, covered with mica-like scales.

Pathogenesis

Psoriasis results from a polygenic genetic disposition and an environmental trigger. Its severity is believed to be genetically determined, and several environmental factors are known to exacerbate it. Key components of the pathogenesis are potential therapeutic targets.

(a) *Activated T lymphocytes* – appear to be important in all phases of the disease process (initiation, maintenance and resolution). Patients with psoriasis who undergo bone marrow transplantation from a healthy donor sometimes experience long-term remission. (b) *T-helper lymphocytes* migrate from blood vessels into the skin, where they interact with antigen-presenting cells and then become activated into a T-helper type 1 phenotype, proliferate and release various cytokines and chemokines which attract and activate T-cytotoxic lymphocytes. (c) *Interferon-α and tumour necrosis factor (TNFα)* are released by immune cells, further promoting inflammation and development of psoriatic lesions. (d) *Epidermal cells overlying the inflammatory process* proliferate and turn over at four times the normal rate, resulting in thickening of the epidermis with overlying scales. In the upper epidermis proliferation of vessels occurs.

Aetiology

Genetic factors – Identical twins have a concordance rate of 50–70%. There is a strong association of the disease with HLA-Cw6, and weaker associations with HLA B13, B17 and DR7. Both HLA associations and a family history of psoriasis are more common in patients who develop the disease before 40 years of age.

Environmental factors – Attacks of psoriasis can be precipitated or aggravated by stress, infection (streptococcal, HIV), pregnancy, trauma, drugs (chloroquine/antimalarials, lithium), alcohol, tobacco smoking, sunlight.

Morphology

Psoriasis vulgaris (chronic plaque psoriasis) is the most common form. The primary lesion is a plaque which is sharply marginated, indurated, erythematous (modified by skin colour). The plaque variable in size may be surrounded by a hypopigmented halo. Initial lesions are discoid but may merge to form polycyclic or geographic plaques.

The plaque surface is usually scaly (Fig. 39) and gentle scratching may produce a silvery appearance from the lifting of numerous tiny scales. Lifting larger scales may result in capillary bleeding (*Auspitz sign*) because the elongated capillaries almost reach the skin surface.

Psoriatic plaque with well-defined edge

The *Koebner's phenomenon,* in which psoriatic lesions tend to develop at sites of trauma (e.g. a surgical wound or a trivial scratch, abrasion or burn) is a helpful diagnostic feature when seen. It also occurs in lichen planus, but not in eczematous dermatoses.

Variants

1. ***Morphological***
   - **Guttate psoriasis** – occurs in children and adolescents, small erythematous papules appear in several guttate which clear within a few weeks or evolve into plaque psoriasis.
   - **Rupioid psoriasis** – Instead of scaling the surface of the plaques is covered by hard, thickened firmly

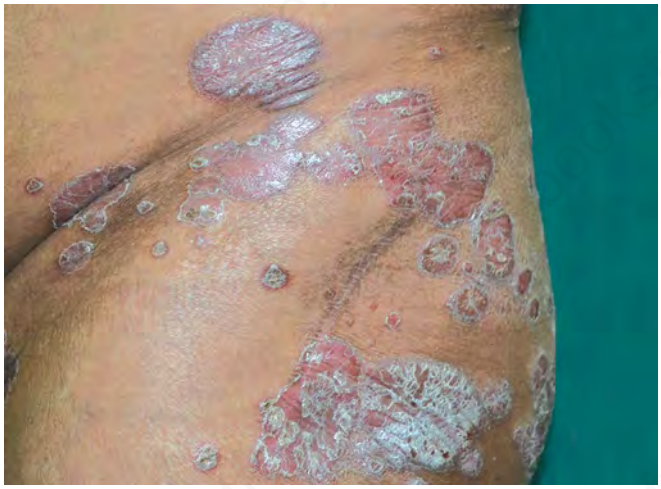


Fig. 39: Psoriatic plaque with well-defined edge

adherent keratin plaques. Such lesions are classically seen in Reiter's syndrome.

2. ***Modification by site***
   - **Flexural psoriasis** – Well-defined erythematous lesions, mostly in elderly females in groins, axillae, inflammatory folds, vulva, gluteal cleft.
   - **Scalp psoriasis** – Sharply defined indurated scaly plaques. Scaling may be massive, especially in the occiput, may spread to forehead and nape of neck (Fig. 40).
   - **Psoriasis of palms and soles** – Bilateral, symmetrical, well defined plaques, scales may be adherent unlike loose scales in other parts.
   - **Nails –** Pitting, nail plate thickening, subungual hyperkeratosis, onycholysis oil spots (Fig. 41).
   - **Joints** – Arthritis types – (a) Asymmetrical oligoarthritis involving commonly joints of hands and feet. (b) Distal interphalangeal arthritis. (c) RA – like seronegative, symmetrical arthritis. (d) Axial arthritis – Spondylitis, sacroiliitis and with or without peripheral joint involvement. (e) Arthritis mutilans – severe, deforming arthritis of fingers and toes.
   - **Penile psoriasis** in uncircumcised males. No scaling on glans, lesions erythematous, well-defined. In circumcised males lesions similar to lesions at other sites.

Complications

- Erythrodermic psoriasis precipitated by irritant effect of topical therapy or withdrawal of steroids in therapy. Plaques merge and skin becomes erythematous with marked scaling.
- Pustular psoriasis – Precipitating factors same as above. Pustulation can be localized or generalized with red erythema followed by appearance of small superficial pustules, which become confluent. New pustules appear as the older ones are crusting. Constitutional symptoms like high fever, tachypnoea.

Management

As a general rule, topical treatments are safest. Phototherapy and systemic agents should be used only when topical treatments are ineffective.

I. Topical therapies

1. *Topical corticosteroids* – Potent category (e.g. clobetasol) applied bd to localised lesions. Overnight or occlusive therapy will initiate involution in most cases. Hydrocolloid dermatological patches can be applied over steroids on localised psoriatic plaques for 2 to 7 days. As lesions subside, use of occlusion on is decreased, and bland emollient applied. After lesions have flattened, corticosteroids can be applied in bursts (e.g. several days on and several days off). Injection of intralesional corticosteroids (e.g. Triamcinolone) beneath isolated chronic plaques will cause involution within 7 to 10 days.
2. *Topical Vitamin D analogue*s – Calcipotriol ointment, cream or lotion is applied bd. Dose should not exceed 100 g/week because of risk of hypocalcemia and kidney stones.
3. *Topical tazarotene* gel and cream (0.05% and 0.1%) to minimise irritation – (i) Tazarotene should be applied to the affected skin only at bedtime, with protection of normal skin with vaseline. (ii) Apply a mid to high

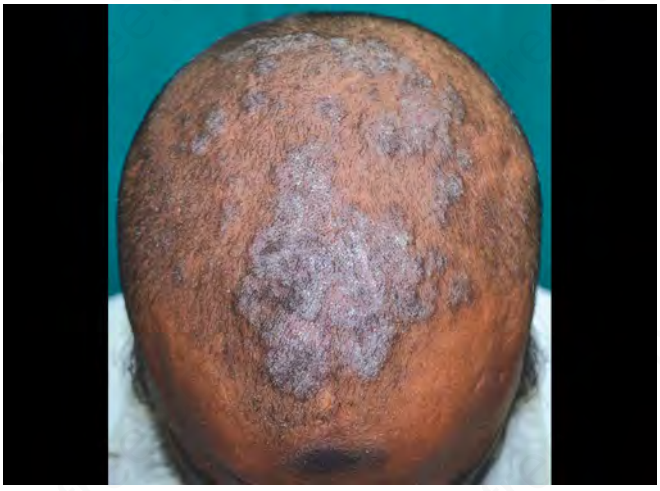


Fig. 40: Scalp psoriasis

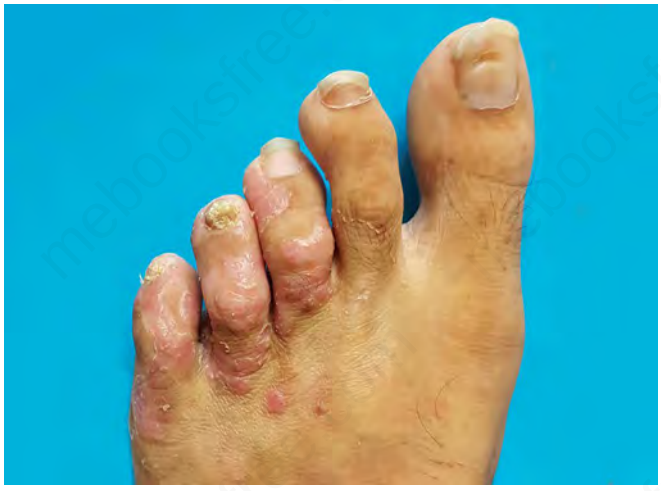


Fig. 41: Psoriasis of toes with onycholysis

potency steroid in morning. Tazarotene combined with UVB phototherapy is more effective than phototherapy alone.

4. *Coal tar therapy* (3–6% crude coal tar) can be combined or alternated with topical corticosteroids. The patient should apply a formulation overnight and be exposed to UVL the following morning, or apply a corticosteroid cream with or without occlusion during the day tar overnight, and UVA exposure in morning.
5. *Other topical agents* – (i) Salicylic acid 2–10% helps to remove scales and crusts and may be used along with corticosteroid or anthralin therapy. (ii) Anthralin is effective for treatment of discrete lesions consisting of thick plaque. Disadvantage is primary irritation and staining of skin and clothes. (iii) Topical tacrolimus or pimecrolimus may be effective in intertriginous and facial psoriasis because of better absorption.
6. *Exposure to sunlight or UVB* from the point of mild erythema and induce flattening or clearing of many lesions. An excimer lens with intense radiation can clear a plaque of psoriasis with even one treatment, although usually 4 to 8 treatments are required.

Treatment of Severe or Widespread Involvement

1. Aggressive UVB pototherapy 5 times a week or daily most effective single agent therapy.
2. Photochemotherapy – Psoralen plus PUVA – 10 to 20 treatments are required. Psoriasis often recurs after stopping treatment and twice monthly treatment is required to keep most patients free of the disease.
3. Combined therapy for clearing resistant and wide spread disease include PUVA-UVB, retinoid-PUVA, retinoid UVB, methotrexate PUVA – Twice weekly UVB with one weekly methotrexate for 8 week.

II. Oral systemic agents

1. Acitretin – A synthetic vitamin A is effective in pustular, guttate and erythrodermic psoriasis. Dose 10–20 g/day with maximum 50 mg/day. Side effects – Elevation of triglycerides, hair loss, thinning of nails, xerosis.
2. Antimetabolite therapy – (i) Methotrexate oral or IM. Dose – Initial 7.5 mg/week with increase of 2.5 g/week as tolerated. (ii) Cyclosporine 3.5 g/kg/day.

   Treatment schedule – Rotate therapies to try and minimise adverse effects of each, e.g. UVB, PUVA, methotrexate, acitretin and cyclosporine.

   Other agents – (i) Mycophenolate mofetil 500 mg qds Side effects – herpes zoster, neutropenia, GI symptoms. (ii) Fumaric acid. (iii) Calcitriol.
3. Biological therapies – (i) Alefacept 15 mg/week IM for 12 weeks. If CD4 count falls < 250 cells/μL, it should be discontinued. (ii) Efalizumab 1 mg/kg/wk sc inj. Worsening of psoriasis may occur after discontinuation of therapy or in unresponsive patients during therapy. (iii) Etanercept 50 mg sc twice a week for 12 weeks, followed by maintenance of 50 mg/week. (iv) Infliximab.

Scalp care. (i) Mild case – Tar shampoo (10%) or steroid containing shampoo. (ii) Severe case – Removal of scales and application of keratolytic gel and then covered with occlusive plastic shower cap for several hours or overnight. This will loosen the scales, after which steroid lotion should be applied under a shower cap for the night or without occlusion during the day.

Nail care. (i) Removal of subungual debris and application of corticosteroids under occlusion. (ii) Injection of triamcinolone (0.1 mL of 3 mg/mL) into the nail bed at 2–3 week intervals. The procedure is painful and a ring block can be utilized to minimize pain.

Second-line Therapy for Psoriasis

Indications:

- Topical therapies fail to control the disease
- More extensive disease
- Co-existing psoriatic arthropathy
- Erythrodermic or generalized pustular psoriasis (both associated with a mortality of 5–10%)

Special Groups

Psoriasis in childhood. Topical corticosteroids should be avoided. Phototherapy is effective, but exposure to ultraviolet light is kept to a minimum. Retinoids or cyclosporine are the systemic agents of choice.

Psoriasis in pregnancy. Retinoids are best discontinued in female patients after puberty because of the risk of teratogenicity. Pregnancy should be avoided within 2 years of taking acitretin.

LICHEN PLANUS

It is an inflammatory disorder of the skin and mucous membrane, of unknown origin. The term lichenoid is applied to eruptions that clinically resemble lichen planus, or have a similar histology, in particular a heavy lymphocytic infiltrate immediately under the epidermis, the basal layer of which suffers the most damage. Lichenoid eruptions may be caused by drugs, or may occur as a part of chronic graft-versus-host disease. The term lichen planus is applied to the more common idiopathic form.

Description – Shiny, flat-topped, violaceous, polygonal papules of varying size, clustered around on the wrists

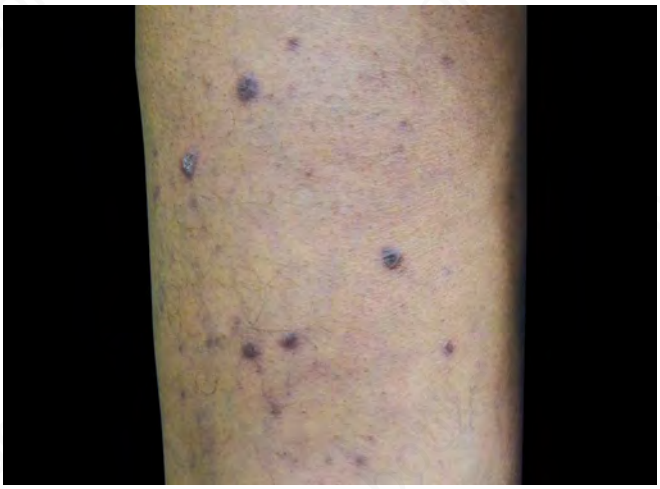


Fig. 42: Lichen planus

(Fig. 42). Irregularly linear or reticulate white striae (Wickham's) are often seen in the papules. The lesions are usually itchy sometimes intensely so, but are occasionally asymptomatic. The inflammation usually subsides within 2 years and is commonly followed by post-inflammatory pigmentation.

Mucosal lichen planus in form of whitish papular lesions, linearly disposed, may crisscross to form a lacy pattern, coalescence of papules may result in plaque formation. It accompanies cutaneous disease in about 50% of patients, and is common alone.

Distribution – Usually flexor areas are more affected. In males the genitals may also be involved in about 10% of patients.

Variants

- Persistent hypertrophic lesions, usually on the lower legs
- Scalp lesions may cause scarring alopecia
- Bullous lichen planus – Blistering tends to occur within typical lesions in lower legs
- Erosive disease may affect the gingiva, vagina and vulvar vestibule (vulvo-vaginal-gingival syndrome of Hewitt and Pelisse). Severe vaginal stenosis may occur.

Treatment – Milder cases may require no treatment. For localized itchy lesions strong topical steroid (e.g. clobetasol propionate).

Systemic therapy – If distressing itch, extensive eruption, destructive nail involvement, or erosive mucosal lesions. Prednisolone 20 mg/day reducing according to response, and cyclosporine 5 mg/kg/day usually for several weeks. The retinoid acitretin produces a slower response, but is a safer drug when long-term control is required. Dapsone may also be given.

Patients with severe, especially erosive mucosal lichen planus, should be followed up for early detection of carcinoma.

Lichenoid drug eruption – It may be caused by thiazides, antimalarials, gold, NSAIDs, β-blockers and captopril. Clinical picture may be atypical with psoriatic features. Lichen planus of the mouth may be drug-induced, or be a reaction to dental materials.

Graft-versus-host disease. About 10% of patients with allogenic bone marrow transplants develop chronic graft-versus-host disease. The earliest skin manifestations are usually lichenoid.

14. BLISTERING DISORDERS

See Table 23 for the classifications of blistering disorders.

Blistering results from damage to cell-cell or cell-matrix adhesion resulting in accumulation of fluid in the extracellular space. Causes of blistering are given in Table 24.

DIAGNOSIS OF BLISTERING DISEASES

History

- Age of onset (genetic disease usually presents in infancy or childhood)
- Exposure to hazardous chemicals or sunlight
- Previous or current infection
- Drug ingestion
- Duration and course of blistering

Examination

- Mucosal involvement (suggests systemic, possibly immunological disease)
- Evidence of infection (e.g. herpes zoster)
- Morphology of lesions (background erythema, excoriations, scarring, intact blisters or just erosions)
- Distribution (linear – insect bites, buttocks and elbows – dermatitis herpetiformis, dermatomal – herpes zoster)

Laboratory Investigations

If infection is suspected, specimens should be taken for bacteriological and virological culture. In cases with a genetic and/or immunological basis, skin biopsies.

Skin biopsy – An ellipse biopsy taken from the edge of a fresh blister to see the level of the split, a vital feature in diagnosis.

Table 23: Classification of blistering disorders
I. Intraepidermal (Bulla within epidermis)
1. *Subcorneal*
– Bullous impetigo
– Staphylococcal scalded skin syndrome
– Pemphigus foliaceus
– Miliaria crystallina
– Subcorneal pustular dermatosis
2. *Spinous layer*
– Herpes simplex
– Herpes zoster
– Miliaria rubra
– Chicken pox
– Dermatitis
3. *Suprabasal*
– Pemphigus vulgaris
– Pemphigus vegetans
II. Subepidermal (Bulla below epidermis)
• Bullous pemphigus
• Dermatitis herpetiformis
• Toxic epidermal necrolysis
• Epidermolysis bullosa dystrophica

Table 24: Causes of blistering
Genetic
• Epidermolysis bullosa
– Junctional (recessive)
– Dystrophic (dominant and recessive)
– Simplex (dominant)
Physical
• Heat and cold
• Irradiation (e.g. ultraviolet light)
• Contact with hazardous chemicals and irritants
• Friction/rubbing
• Oedema on legs
Inflammatory
• Infections
– Staphylococcal (e.g. bullous impetigo caused by Staph. aureus, staphylococcal scalded-skin syn.)
– Streptococcal (including necrotizing fasciitis)
– Herpes simplex
– Herpes zoster
– Hand, foot and mouth disease
– Fungal
• Eczema
• Erythema multiforme (including Stevens-Johnson syn.)
• Insect bites
Immunological
• Bullous pemphigoid
• Linear IgA disease
• Pemphigus (vulgaris and foliaceus)
• Epidermolysis bullosa
• Dermatitis herpetiformis
• SLE
– Lichen planus
– Pemphigoid gestationis
– Porphyria cutanea tarda
Drug reactions
• Fixed drug eruptions
• Pemphigus
– Erythema multiforme including Stevens-Johnson syndrome
– Photosensitive reactions
– Pemphigoid
– Toxic epidermal necrolysis

- *Direct immunofluorescence* – Most immunological causes can be defined and the pattern is often diagnostic.
- *Electron microscopy of the skin* may be helpful in distinguishing between junctional and dystrophic epidermolysis bullosa when immunofluorescence testing is inconclusive.
- *Indirect immunofluorescence* of circulating antibodies can be demonstrated in blister fluid or serum. Further information can be obtained about the antibody binding site which may avoid need for electron microscopy.

BULLOUS PEMPHIGOID

Autoimmune disease common in elderly. Two target antigens have been identified – a 230 kD protein (major antigen) located in the dense plaque of the hemidesmosome, and a 180 kD protein (BP 180) which is collagen XVII traversing the plasma membrane and linking to the anchoring filaments.

Description – Typical appearance is of large, tense blisters (Fig. 43) up to 3 cm diameter on an erythematous base. In early stages of the disease a pruritic urticarial rash

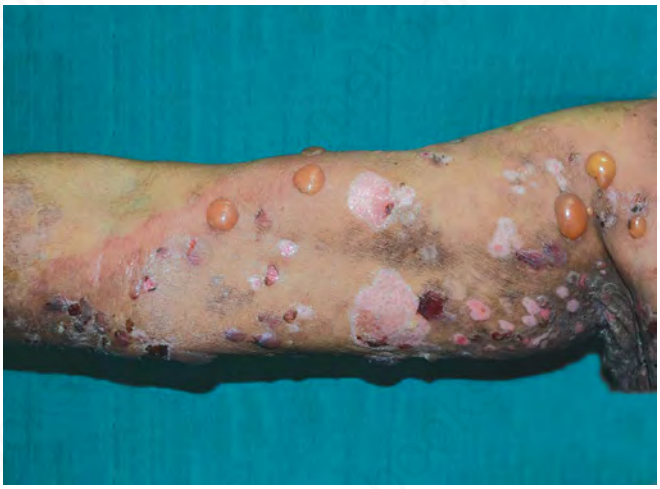


Fig. 43: Tense blisters in bullous pemphigoid

may be the only visible sign. The blisters may be broken as a result of excoriation.

Distribution – Usually starts on the limbs and often spreads to the trunk. Mucous membranes are often involved – oral cavity, anus, vagina and oesophagus.

Cicatricial pemphigoid is a variant of bullous pemphigoid in which mucous membrane involvement only occurs, often with scarring.

Diagnosis – (a) Histology – Split at level of basement membrane with mixed inflammatory infiltrate rich in eosinophils at the base. (b) Direct immunofluorescence of perilesional skin shows a linear band of immunofluorescence with IgG and/or C3 at the basement membrane zone. (c) Serology – Circulating IgG or C3 antibody to the basement membrane is found in 75% of patients.

Treatment – In mild cases, potent topical corticosteroids. Prednisolone 30–60 mg/day in early stages. Cyclosporine is added for its corticosteroid-sparing effect. The disease often remits spontaneously after 2–5 years and treatment can then be withdrawn. Although morbidity is considerable, mortality is low. Dapsone is a useful adjuvant and allows an easy tapering of steroids.

PEMPHIGUS

Autoimmune disease, characterised by acantholysis, induced by deposition of intracellular autoantibodies.

Classifications

The level of split forms the basis of subdivision into:

- Pemphigus vulgaris – Splitting just above the basal layer
- Pemphigus foliaceus – Superficial epidermal split with short-lived blisters.
- Pemphigus vegetans – Split is suprabasal
- Pemphigus erythematosus – Split in granular layer or just below stratum corneum

Clinical Features

Pemphigus vulgaris (a) *Skin lesions* – Development of flaccid, fragile blisters which rupture to form painful erosions. Application of tangential pressure on normal skin in pretibial region gives rise to new bulla (Nikolsky sign) or to existing bulla causes spread of the bulla (bulla spread sign). Site – Scalp, face, flexures and trunk. (b) *Mucosal lesions* mostly in oral mucosa – Painful erosions with shedding of mucosa which looks ragged. Skin and mucosal infections get secondarily infected.

Pemphigus foliaceus – Superficial bullae which soon rupture to form large areas of scaling and crusting. Initial distribution on face and trunk becomes generalized resulting in erythroderma.

Pemphigus vegetans – Heaped up vegetating peripherally spreading lesions. Sites – Groins, axillae, angles of mouth. Mucosa may be involved.

Pemphigus erythematosus – Variant of pemphigus foliaceus but less severe. Dry, hyperkeratotic, scaly lesions on face (malar regions).

Pemphigus variants – (a) Paraneoplastic – Polymorphic skin lesions, painful oral mucosal lesions, associated with lymphoma, thymoma. (b) Drug-induced – Rifampicin, penicillamine, captopril *Cl. Fs.* Like PF or PV.

Investigations and Diagnosis

(a) Tzanck smear from erosion or floor of bulla reveals acantholytic cells. (b) Direct immunofluorescence shows intracellular deposits of IG, giving a fish net appearance. (c) Serology – Presence of IG antibodies with titres correlating with disease activity.

Treatment

1. Specific – (a) Corticosteroids – Prednisolone 1–2 µg/kg body weight per day with gradual tapering or Betamethasone 1–2 mg/kg or IV Dexamethasone for 3 consecutive days every month. (b) Immunosuppressive therapy – as steroid sparing therapy in patients with adverse effects or resistant to steroid. Azathioprine 2–3 mg/kg till suppression, 1 mg/kg as maintenance or Methotrexate 15–25 µg/wk or Cyclophosphamide 50–200 mg/d PO. (c) Other therapies - Mycophenolate mofetil,

high dose or IG IV, plasmapheresis, biologic response modifies, extracorporeal photochemotherapy.

2. Supportive treatment – Antibiotics for cutaneous lesions and anticandidal agents for mucosal lesions. Water and electrolyte balance.

DERMATITIS HERPETIFORMIS

Is primarily a disease of young adults. There is a strong association with HLA B8, DR3 and DQ2. The role of gluten sensitivity is established. There is a close association with coeliac disease.

Description – A vesicular rash typically occurs on an erythematous base and vesicles are often excoriated (Fig. 44). Intense pruritus is a prominent feature and may precede other symptoms.

Sites – Buttocks, extensor aspects of elbows and the knees, and sometimes the scalp and shoulders.

Diagnosis – (a) Histology – Skin biopsy shows subepidermal blister formation with collections of neutrophils, forming microabscesses in the dermal papillae. (b) Direct immunofluorescence of uninvolved skin shows a granular deposit of IgA below the basement membrane zone confined to dermal papillae; this is diagnostic. (c) Serology – Antigliadin and antiendomysial antibodies are often present.

Treatment – Dapsone 50–200 mg/day produces prompt response. 2 weekly monitoring of blood, later monthly. If haemolysis is severe alternative drug (e.g. sulphamethoxypyridazine) can be tried.

Gluten-free diet should be started on all patients, and continued for life, to prevent a relapse, and the risk of lymphoma.

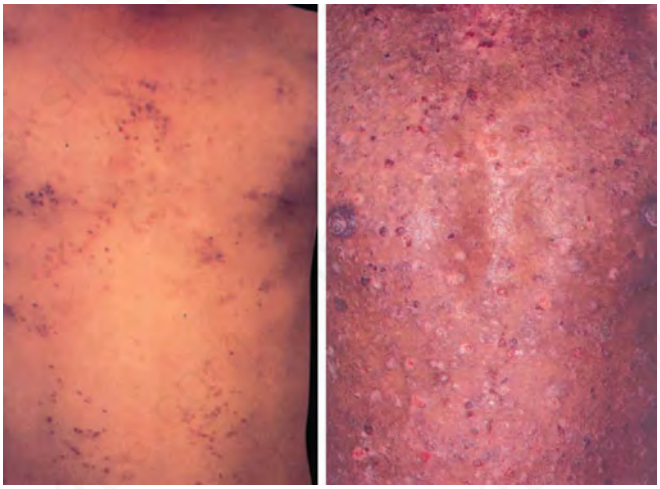


Fig. 44: Dermatitis herpetiformis

PEMPHIGOID GESTATIONIS

Is an uncommon disease associated with pregnancy, or occasionally with trophoblastic tumors.

Clinical features – Initially, urticated plaques appear on the abdomen and rapidly become more widespread with blister formation. Onset is typically in the second trimester. An immediate post-partum flare is common.

Direct fluorescence shows a linear band with IgG at the basement membrane.

Treatment – Oral corticosteroids, which may need to be continued post-partum, but most cases resolve within 2 months of delivery.

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is a group of uncommon mechanobullous disorders characterized by blisters and erosions resulting from trivial trauma. There are three principal types, each with a different level of split.

Junctional EB – Subepidermal split through the epidermal site of the basement membrane. It presents at or shortly after birth and may be fatal. The anchoring filaments are abnormal as a result of mutations a6b4 integrin, BP180 or laminin 5 molecules. Nikolsky's sign is absent.

EB simplex – It represents a collection of diseases with a suprabasal split. It presents in early childhood. Blisters occur on knees and elbows initially, and later on hands and lower legs. Responsible mutations are in keratins 5 and 14.

Dystrophic EB – Subepidermal blister below the dermoepidermal junction. Scarring is common and often leads to mutilation of the extremities. It is caused by mutations in collagen VII, the anchoring fibril protein.

Treatment – None effective known. Antenatal diagnosis of the more severe forms can be done through chorionic villous sampling. Genetic counselling to affected families.

Chronic bullous disease of childhood is an immune-mediated blistering disorder. Tense bullae, with development of new blisters around healing bullae (string of pearl appearance). Sites – Around body orifices. *Tr.* – Dapsone/erythromycin, if necessary steroids.

15. URTICARIA AND ANGIO-OEDEMA

Urticaria ('nettle rash, 'hives') presents with short-lived, itchy wheals which may be pale or pink in the centre, surrounded by a red flare. Deeper swellings of the skin or submucosa are termed 'angio-oedema'. They are usually

in the mouth, on the eyelids or on the genitals, but may occur anywhere on the skin.

Pathogenesis – Urticaria is caused by transient leakage of plasma through small blood vessels, usually as a result of release of histamine through skin mast cells. There are many causes of this including type I hypersensitivity reactions. Histamine also causes itch, by stimulating nerve receptors. Other mediators causing vasopermeability include kinins in hereditary angioedema, and leukotrienes in pseudoallergic reactions caused by aspirin and NSAIDs.

PROVOKING CAUSES

Drugs: Penicillin, sulphonamides, aspirin, phenytoin, salicylates, indomethacin, foreign sera, insulin, ACEIs.

Foods: Milk, moong dal, masoor dal, eggs, peas, fish.

Physical causes – Dermographism, pressure urticaria, cold or heat or solar urticaria, cholinergic due to decrease in core body temperature, exercise-induced.

Contact urticaria – Contact with, e.g. onion, nitrogen, mustard.

Inhalants: Pollens, fungi, insecticides, house dust.

Infections and infestations: Chronic septic focus, UTI, virus infection, candida infection, protozoal and helminthic infections.

Food additives: Yeasts, citric acid, azo dyes, benzoic derivatives.

Emotional stress especially in cholinergic urticaria.

General medical disease. Lupus erythematosus, reticuloses, polycythemia, macroglobulinemia, endocrine disorders such as thyrotoxicosis. Premenstrual aggravation of urticaria as a result of progesterone sensitivity.

TYPES OF URTICARIA AND INVESTIGATIONS (SEE TABLE 25)

Ordinary urticaria. Recurrent urticaria is termed 'ordinary' if there is no predominant physical cause or underlying small vessel vasculitis. Attacks may occur daily or less frequently. Wheals (Figs. 45 and 46) generally last 2–24 hours, are often numerous, and may occur on any part of the skin including scalp, palms and soles, where they can be painful rather than itchy. They vary in size from < 1 cm to many centimetres across, and may coalesce. Nonspecific symptoms (lassitude, indigestion) may accompany severe attacks, but wheezing is not a feature. Onset is often abrupt and unexpected, but there is sometimes a history of preceding viral infection, immunization, eating an unusual food (e.g. fish, fruit, nuts) or drug therapy (e.g. aspirin, penicillin).

Blood tests are negative. Tests for specific IgE (UniCAP immunoassay often termed RAST) may be useful for confirming the cause of allergic urticaria.

Physical urticaria. Physical urticarias are defined by the triggering stimulus:

Immediate dermographism can be elicited by stroking the skin firmly with a blunt instrument.

Cholinergic urticaria by overheating to the point of sweating (sweat glands have cholinergic sympathetic innervation).

Cold urticaria by contact with ice or generalized chilling. Cutaneous mast cells degranulate in response to these stimuli; the mechanism is unclear. Some physical challenge tests are necessary to confirm the diagnosis.

Contact urticaria – (a) *Immunological contact urticaria* involves binding of percutaneous allergen to specific IgE in previously sensitized individuals. Localized whealing occurs within 10 minutes. Atopic patients are susceptible. (b) *Non-immunological contact urticaria* from direct mast cell degranulation or eicosanoid release is probably more common. Preservatives and fragrancies in cosmetics may cause stinging, itching, and burning. Food preservatives (e.g. benzoic acid, sorbic acid) and flavourings (e.g. cinnamic aldehyde) may cause contact urticaria around the mouth.

Table 25: Types of urticaria and investigations

Type	*Investigations*
Ordinary urticarial	
Acute (<6weeks)	Skin-prick test/food RAST*
Chronic (>6weeks)	Autologous serum skin test
Physical urticarial	
Cold/cholinergic/ dermographism	Ice/overheating/skin stroking
Delayed-pressure	Sustained local pressure
Contact urticaria	
Immunological	
Non-immunological	
Urticarial vasculitis	Skin-prick test/RAST
	Skin-rechallenge
Angio-oedema without wheals	
Idiopathic	Skin biopsy, serum C3, C4
C1 inhibitor deficiency	
Drug-induced (angiotensin-converting enzyme inhibitors, aspirin)	C1 esterase inhibitor, C4

* Only when indicated by the history

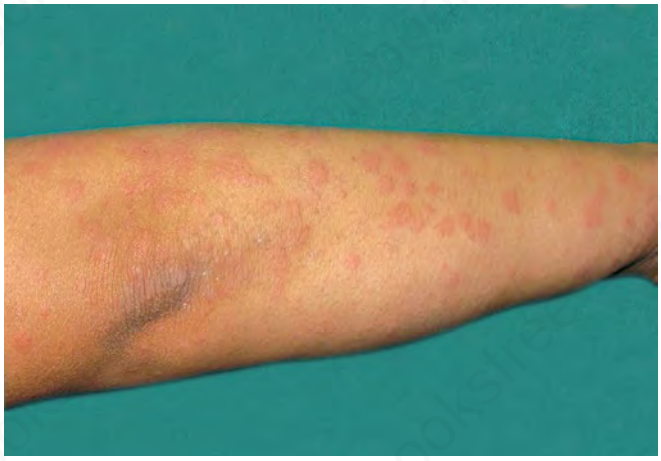


Fig. 45: Urticaria

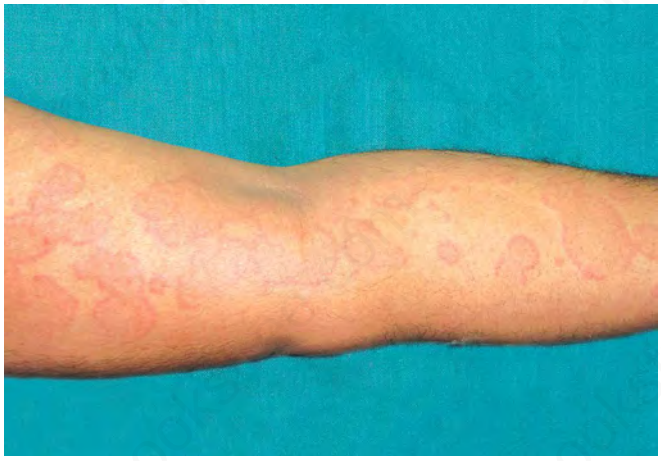


Fig. 46: Chronic urticaria

Urticarial vasculitis is an uncommon systemic disorder. Patients have small vessel vasculitis caused by immune complex deposition. Skin lesions may be indistinguishable from other forms of urticaria, or may resemble erythema multiforme. They often last 2–3 days and fade with a bruised appearance. They may burn rather than itch. Patients may feel unwell with malaise and arthralgia, and associated renal, pulmonary or neurological disease must be excluded. Skin biopsy shows venulitis, ESR is raised, and some patients are hypocomplimentaemic.

Angio-oedema consists of transient episodes of local subcutaneous and dermal oedema. It occurs in ordinary, physical and vasculitic urticaria but may also occur without wheals.

Description – Sudden diffuse, soft, non-tender swellings, which may be like urticaria – pale or erythematous.

Distribution – Common sites are eyelids and lips (Fig. 47). Upper extremities, feet, scrotum, vulva and penis may be involved.

Associated features – Idiopathic angio-oedema is frequently associated with urticaria. Hereditary angio-oedema is a rare autosomal dominant disorder in which patients suffer from symptoms related to subcutaneous and GI angio-oedema. These patients are at risk of sudden death due to laryngeal oedema.

Investigations – are required to exclude hereditary and acquired C_1 esterase inhibitor deficiency. Measurement of C_4 is a useful screening test; it is reduced in both type I hereditary disease (reduced absolute levels of C_1 inhibitor) and the less common type II hereditary disease (normal quantitative C_1 inhibitor on immunochemical assay but reduced function).

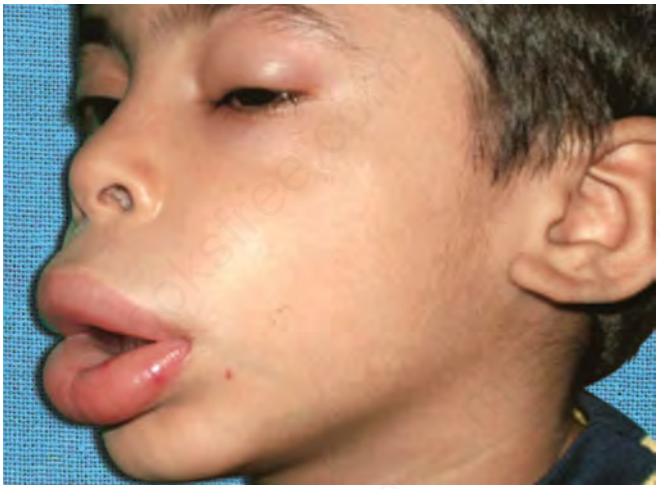


Fig. 47: Angioedema

MANAGEMENT

Histamine-mediated urticaria

1. Remove identifiable cause
2. Non-drug therapy
   - Explanation and information
   - Cooling lotions (e.g. calamine, 0.5% menthol in aqueous cream)
   - Avoid aspirin, NSAIDs, codeine, ACEHs
   - Minimize stress, over-eating, alcohol
   - Exclusion diet when indicated by history
3. Pharmacological therapy

   First line – All patients
   - Non or low-sedating antihistamine (cetirizine or loratadine 10 mg/day)

- If little or no response, add sedating H_1 antihistamine at night
- If little or no response add H_2 antagonist (e.g. ranitidine)

Second line – special indications

- Prednisolone 0.5 mg/kg stat or a tapering regimen over 1–2 weeks (in severe or delayed pressure urticaria) for short-term use
- Adrenaline 0.5–1 mL of 1:1000 Im or SC in severe throat angio-oedema

Third-line – specialist use only

- Immunotherapies – plasmapheresis or IV immunoglobulin, or cyclosporine (if severe refractory autoimmune urticaria)

Immune complex mediated urticaria – Antihistamines are often ineffective in urticarial vasculitis. Corticosteroid-sparing drugs to minimize or replace long-term oral corticosteroid exposure – dapsone 75–150 mg/day, indomethacin 25–50 mg t.d.s., hydroxychloroquine 200–400 mg/day, azathioprine 2–2.5 mg/kg/day, and colchicine 0.5–2 mg/day. Management of chronic urticaria is removal of identifiable cause followed by non-drug therapy or pharmacological therapy.

Hereditary angio-oedema – Recurrent angio-oedema caused by C_1 esterase inhibitor deficiency can often be prevented by prophylactic low-dose anabolic steroids (e.g. stanozolol 2.5–10 mg/day), which increase functional inhibitor levels.

Antifibrinolytic agent tranexamic acid 1–1.5 g b.d. or t.d.s. is used for prophylaxis and treatment of acute episodes. Severe angio-oedema of the mouth or bowel should be treated as early as possible with IV infusion containing 3 vials of freshly reconstituted C_1 esterase inhibitor concentrate or, if this is unavailable, 3 units of fresh frozen plasma. Antihistamines have no effect.

Urticaria pigmentosa is a skin disease in which clinical features are due to a pathological increase in dermal mast cell numbers.

Childhood urticaria pigmentosa presents with number of brownish dermal papules and plaques widely distributed over the body, when rubbed these become urticated (Darier's sign). Pruritus is common and in severe cases wheezing, diarrhoea and syncope. Lesions may become bullous.

Adult urticaria pigmentosa presents with an insidious onset of monomorphic pigmented maculopapular lesions, sometimes with prominent telangiectasia on trunk and limbs. Systemic symptoms include weight loss, bone pain (osteoporosis or osteosclerosis), abdominal pain (peptic ulcer). Palms and soles are usually spared. Mucous membranes rarely affected. Episodes of flushing may occur after rubbing the skin or following intake of alcohol.

Investigations – Skin biopsies may not be diagnostic unless special tests for mast cells are performed.

Tr. – Avoidance of trigger factors including drugs like morphine and codeine and alcohol. Administration of H_1, H_2 antihistamines is helpful.

16. PRURITUS

Pruritus means 'itch', but the term generalized pruritus is usually applied when no causative primary skin disease can be seen. See Table 26 for the causes of generalized pruritus.

TREATMENT

a. Specific treatment depends on the cause, e.g. cholestyramine for cholestatic itch.

b. Nonspecific – Sedation, antihistamines and cooling applications, e.g. lacto calamine, bland emollients for dry skin.

LOCALIZED PRURITUS

Lichen simplex – Lichenification is a form of eczema characterized by epidermal hyperplasia and exaggeration of skin markings and results from repeated scratching or rubbing. It commonly complicates other forms of eczema or other causes of itch, but in their absence it is termed lichen simplex. An itch-scratch cycle develops, which can usually be broken by explanation, a strong topical corticosteroid and sometimes occlusive bandaging.

Pruritus ani and pruritus vulvae. The following are common causes, some of which may coexist.

- Simple irritancy due to excessive dampness from obesity, prolonged sitting or poorly absorbent clothing, urinary incontinence, faecal soiling, vaginal discharge, overuse or poor rinsing of soap.
- Local disorders (e.g. piles, infections, worm infestations, warts, occasionally neoplasm). Diabetes predisposes to candidiasis.
- Primary dermatoses include microbial intertrigo, psoriasis, lichen sclerosis.
- Secondary complications like allergic contact dermatitis from medicaments or toiletries, lichenification, and secondary bacterial or candidial infection.

A few patients in whom physical causes have been excluded, may require psychiatric treatment.

Table 26: Causes generalized pruritus
Dermatological causes –
1. Xerosis (asteatosis, dry skin) – pruritus especially in elderly
2. Physical urticarias
3. Scabies, dermatitis herpetiformis, pediculosis, fibre glass dermatitis, atopic eczema, lichen planus
Systemic causes –
1. Liver disease – Biliary obstruction, primary biliary cirrhosis, chronic liver failure
2. Endocrine disorders – Diabetes mellitus, hyperthyroidism, hypothyroidism, hypoparathyroidism
3. Iron deficiency
4. Polycythemia vera
5. Reticuloses – Hodgkin's disease. In other neoplasms pruritus may be a feature of advanced disease
6. Drugs – Opiate and cocaine abuse, belladona alkaloids, antidepressants, CNS stimulants, niacinamide, cimetidine, antimalarials, psoralen photochemotherapy
7. Parasitic infestations – Trichinosis, onchocerciasis and schistosomiasis
8. HIV – Severe itch alone or usually associated with identifiable lesions, e.g. itchy folliculitis
9. Autoimmune diseases – SLE, systemic sclerosis, sicca syndrome
10. Neurological disorders – Multiple sclerosis, pre-eruptive herpes zoster, brain tumours, tabes dorsalis
11. Pregnancy
12. Psychological disorders – Delusions (of parasitosis), hypochondriasis, obsessiveness, depression, hysteria
13. Chronic kidney failure
14. Senile pruritus

Other sites

- *Ear* – Fungus infection, chronic otitis media.
- *Eyelids* – Neurodermatitis or contact dermatitis.
- *Nostrils* – Intestinal parasites, brain tumour.

17. DISORDERS OF PIGMENTATION

HYPOMELANOSIS (HYPOPIGMENTATION)

Genetic/Naevoid Factors

Vitiligo **–** It is a pigmentary disorder characterised by circumscribed loss of melanin pigment secondary to melanocyte attrition. It is an acquired, sometimes familial condition, an autoimmune disease in majority. Vitiligo is associated with other autoimmune diseases such as thyroid disease, diabetes mellitus, Addison's disease and pernicious anaemia (Fig. 48).

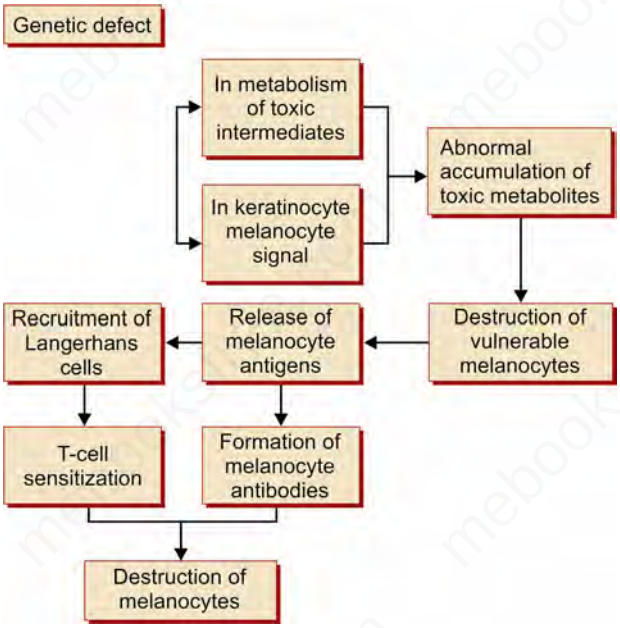


Fig. 48: Mechanism of vitiligo

Pathogenesis – Vitiligo is a complex process involving the melanocytes, epidermal keratinocytes, immune system, and peripheral nervous system (composite hypothesis).

Classification

1. *Localized vitiligo*

   Focal vitiligo – (a) A single macule or a few macules may be localized to skin or mucosa. (b) Segmental distribution of macules.

2. *Generalized* – (a) Vitiligo vulgaris – Common form of vitiligo with symmetrical distribution over trunk and limbs. (b) Lip-tip vitiligo – Only tips of fingers or with mucosal surfaces like lips (Fig. 49), nipples or palms or penis. (c) Acrofacial vitiligo – Involvement of perior-ifacial and distal digits. (d) Universal vitiligo – Involvement of most of the body with only a few areas spared (Figs. 50 to 52).

Treatment

Physical Regime

1. ***Photochemotherapy*** **–** (a) Topical application of ointment or lotion on alternate days (to avoid photosensitivity) followed by PUVA exposure to gradually increasing doses (till mild erythema is seen) of sunlight or artificial source of UVA. (b) Systemic PUVA solution 0.8 MOP, 0.6 mg/kg PO on alternate days followed by gradually increasing doses (till erythema) of

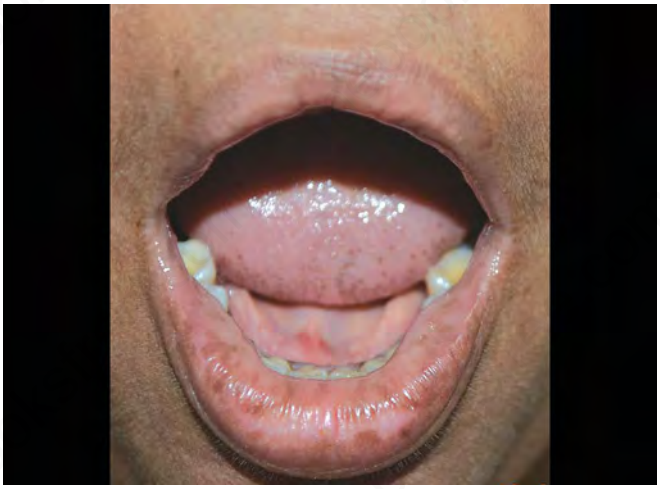


Fig. 49: Vitiligo involving lips

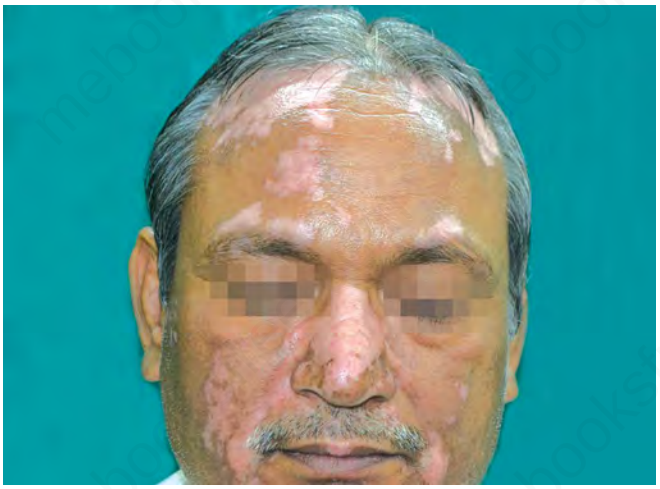


Fig. 50: Vitiligo involving face

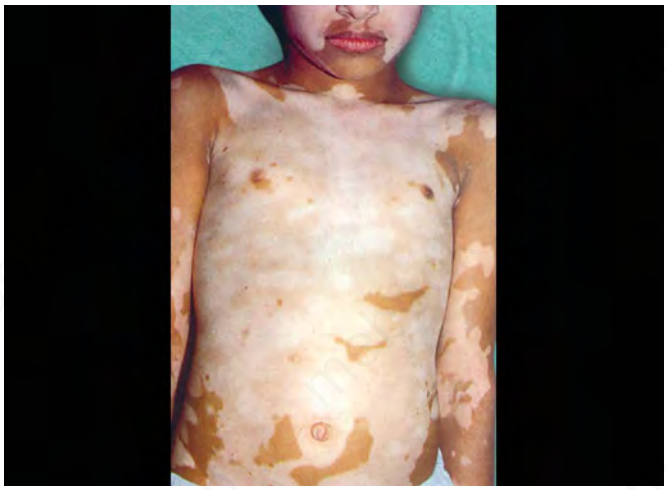


Fig. 51: Vitiligo involving body

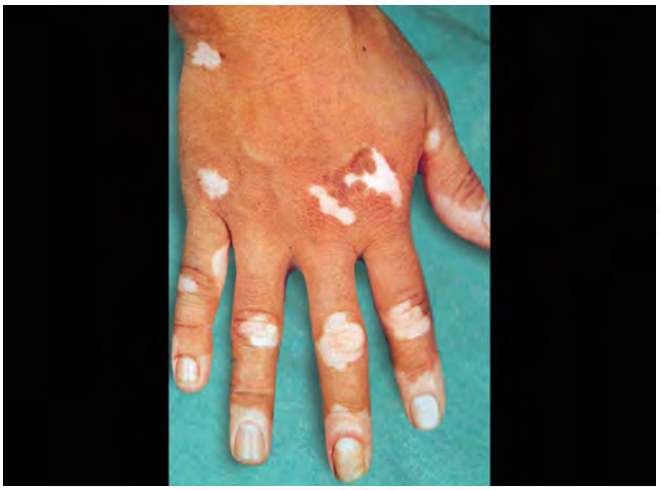


Fig. 52: Vitiligo over hands

sunlight or UVA lamps. Larger dose of UVA is needed here. (c) After exposure to UVA protection of lesions from excessive exposure to sun by using sunscreen like zinc oxide and avoiding peak sunlight.

Result: Slow repigmentation begins in perifollicular area and periphery of lesions and gradually becomes confluent especially on face, neck and hairy region.

Side effects. Phototoxicity results from excessive exposure to sun or UVA. Treatment is to stop and resort to topical or even systemic steroids.

2. ***Phototherapy*** – Narrow band UVA. *Indications* – Extensive disease, children and in pregnancy, and contraindications to gradually increases doses are given from specialized chambers.

Drug Therapy

1. ***Steroids*** – (a) Topical for single lesions or few localized lesions. (b) Systemic. (c) Patient cannot be given photo/photochemotherapy. (d) In rapidly progressive vitiligo, together with PUVA solution. (e) Vitiligo unresponsive to psoralens. Prednisolone 0.5 mg/kg body weight or to minimise cumulative effects of the drug 30–40 mg in two consecutive doses, each week (oral minipulse).
2. ***Other drugs*** – (a) Levamisole may arrest slowly spreading vitiligo. (b) Tacrolimus and pimecrolimus for facial lesions when topical steroid causes side effects. (c) Khellin as adjuvant to photochemotherapy. (d) Placental extract. (e) Depigmenting agents, e.g. monobenzyl ester of hydroquinone.

Surgery – can be used to treat residual vitiligo after medical treatment. Melanocyte transfer, punch grafting, blister grafting, split thickness skin grafting.

Depigmentation – In severe cases that are refractory or cannot be treated for technical or medical reasons, removal of remaining pigment through twice daily application of 20% hydroquinone. Bleached individual however, become more vulnerable to damaging effects of sunlight.

Tattooing – Vitiligo at areas such as lips and fingertips are refractory to above mentioned treatments. These can be masked by tattooing with iron oxide or pigments.

For vitiligo placental extract aqueous solution and alcoholic solution are used locally. Placental extract can also be given parenterally.

3. ***Albinism*** – Melanocytes are present in the skin in normal numbers but no melanin is produced. Two genetically distinct types exist: tyrosinase-negative (type I) and tyrosinase-positive (type II).
   a. ***Piebaldism*** (Partial albinism) is inherited as autosomal dominant disorder. Patient has a white forelock, on central and upper part of forehead. There may be circumscribed and symmetrical areas of hypomelanosis on the trunk, arms and legs. Islands of hyperpigmented macules in the leukodermic patches and in normally coloured is another distinguishing feature. The lesions usually do not change in size or shape.
   b. ***Oculocutaneous albinism*** – In the two main types of this disorder, tyrosinase positive and tyrosinase negative, there is a diffuse absence of normal pigmentation of skin, hair, iris and ocular fundi. Patients with this disease are photosensitive, and epitheliomas may develop in areas of skin exposed to the sun.
4. ***Phenylketonuria*** – is an inborn error of metabolism in which phenylalanine accumulates and impairs melanin biosynthesis. The skin and hair are fair and there is mental retardation.
5. ***Tuberous sclerosis*** – Most children will have between 4-100 hypomelanotic macules identified with Wood's lamp.
6. ***Achromic naevi*** – Here areas of hypomelanosis may be unilateral on any part of the body, or may appear as symmetrical bizarre whorls and streaks in a marble-like pattern. Ectodermal and neurological abnormalities are often present.
7. ***Waardenburg syndrome*** – manifests as a white forelock and cochlear deafness.

Acquired hypomelanosis:

1. ***Endocrine disorders*** – Hypopituitarism, Addison's disease, thyroid disease.
2. ***Chemical depigmentation*** – either occupational or therapeutic, e.g. substituted phenols like hydroquinone or butyl phenol.
3. ***Postinflammatory depigmentation and infections***– Areas of hypomelanosis may occur following the resolution of eczema and psoriasis. Also leprosy and syphilis. Scaly hypopigmented macules seen in pityriasis versicolor.
4. ***Neoplasms*** – A halo of depigmentation may develop around a benign pigmented naevus.
5. ***Miscellaneous disorders*** – Kwashiorkor and chronic protein deficiency, deficiency of vitamin B_{12}, idiopathic guttate hypomelanosis.

Diff. Diag. of hypopigmented/depigmented patch

See Table 27.

Table 27: Differential diagnosis of hypopigmented patch

Cause	*Clinical features*
Vitiligo	Well-defined milky white, nonscaly, variable sized, flat lesion. Hair on lesion of vitiligo may be white. Sometimes depigmented area is separated from normal skin by a thin hyperpigmented rim (trichrome vitiligo)
Leprosy	Sharply demarcated, dry, slightly scaly, concentric anaesthetic patch or reddish hypopigmented patch which may not be anaesthetic. In contrast to vitiligo, anaesthetic patch is never milky white
Tinea versicolor	Scaly, hypopigmented macules. Typical scale is dust-like or furfuraceous. A wood lamp examination may show yellowish fluorescence of affected skin
Pityriasis alba	Most commonly occurs before puberty. Discrete, flat, hypopigmented area with poorly circumscribed or circular or oval outline
Tuberous sclerosis	Small, flat, area with oval or circular outline (Ash-leaf macule). Multiple, small, flesh-colouredpapules around nasolabial fold (adenoma sebaceum) appear around puberty (Fig. 53)

Contd...

Contd...

Cause	*Clinical features*
Post-inflammatory	Hypopigmentation may result from healing of dermal lesions such as tinea corporis, candidiasis or polymorphous light eruption
Halo naevus	Hypopigmented or white lesion which contains a red, brown or black spot in the centre
Piebaldism	Symmetrical, flat, white areas with jagged or geographic borders. Localized areas of hypopigmented hairs (poliosis) may be present
Scleroderma	Drop-like, small, hypopigmented macules around hair follicles (especially face), producing a salt-and-pepper pattern (Fig. 54). Plaques of morphea may be hypopigmented
Incontinentia pigmenti achromicus	Asymmetrical, bizarre whorls or streaks of hypopigmentation in a marbling pattern
Naevus depigmentosus	Birth mark, usually solitary, seen as irregularly shaped, well demarcated, hypopigmented or depigmented patch
Leucoderma	The term includes all depigmented (white) lesions including vitiligo. Causes – (a) Idiopathic (vitiligo). (b) Inflammatory – Lupus vulgaris, discoid lupus erythematosus. (c) Chemicals – Hydroquinone, substituted phenols, adhesives

Fig. 53: Adenoma sebaceum in tuberous sclerosis

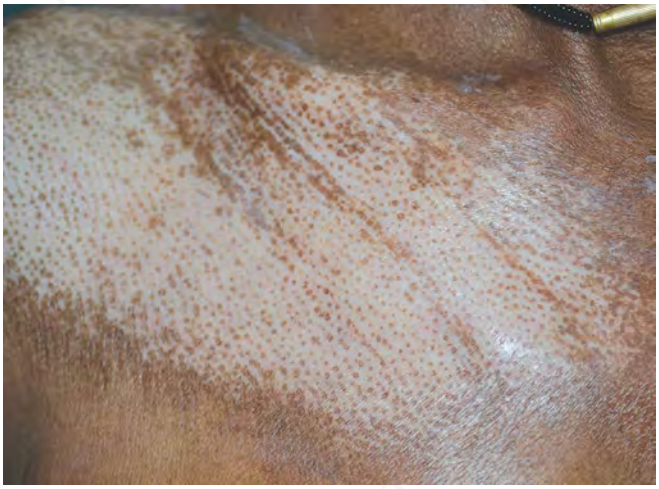


Fig. 54: Salt and pepper skin in scleroderma

HYPERPIGMENTATION

I. **Genetic/naevoid factors**

1. ***Brown colour*** – Hypermelanotic macules may be seen in patients with –
   a. *Neurofibromatosis.* – Cafe au lait macules and axillary freckling.
   b. *Albright's syndrome* – includes polyostotic fibrous dysplasia, endocrine dysfunction and segmental hyper- pigmentation.
   c. *Multiple lentigines* in: (i) Peutz-Jegher syndrome – Pigmented macules on and around lips, on buccal mucosa and on hands and feet. Associated intestinal polyposis. (ii) 'Leopard' syndrome – Generalized lentiginosis, cardiac abnormalities (and abnormal ECG), ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth and deafness.
2. ***Blue or slate-brown colour*** –
   a. *Mongolian blue spot* in sacral region of mongoloid and negroid babies.
   b. *Naevus of Ota* (Fig. 55) around eye.
   c. *Naevus of Ito* on scapular areas.
   d. *Incontinentia pigmenti* (Bloch-Sulzberger type) affects females and presents in the neonatal period with linear group of blisters. These are followed later by characteristic slate-brown streaks and whorls of hyperpigmentation. Dental and ocular defects occur.

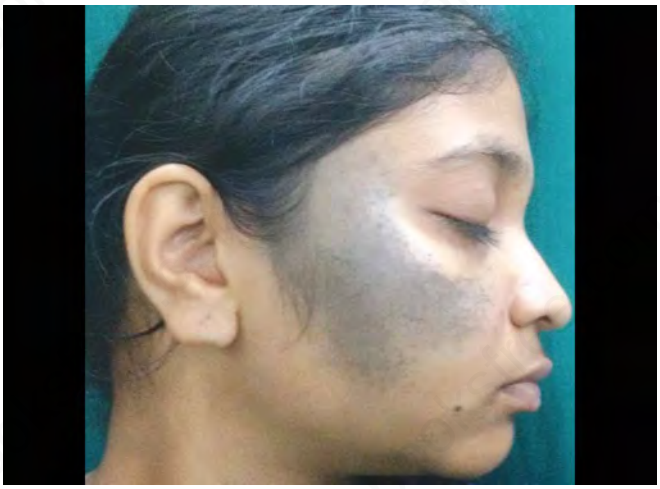


Fig. 55: Nevus of OTA

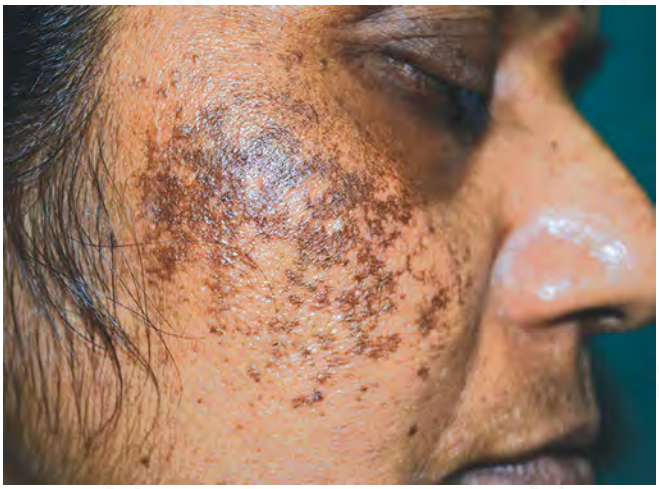


Fig. 56: Melasma

II. **Acquired hyperpigmentation**

1. ***Pregnancy*** – A blotchy hyperpigmentation of the face (melasma or chloasma) affects the cheeks, forehead, nose and chin (Fig. 56). There is darkening of nipples, abdomen and anogenital areas. Similar pigmentation may be seen in women on contraceptive pill. In some women, it can be idiopathic. Idiopathic melasma may also occur in men.
2. ***Endocrine disorders*** – Cushing's syndrome, Addison's disease. Increased pigmentation of Addisonian type may also occur in ectopic adrenocorticotropin syndrome in patients with oat cell carcinoma of bronchus.
3. ***Metabolic disorders*** – (a) Liver disease, e.g. hemochromatosis and primary biliary cirrhosis. (b) Porphyria. (c) Chronic kidney failure.
4. ***Postinflammatory hypermelanosis*** – (a) Resolution of lesions of eczema, lichen planus, lupus erythematosus. (b) Scleroderma. (c) Phytophotodermatitis – Pigmentary reaction of the skin to light, potentiated by psoralens in plants. (d) Berloque dermatitis due to perfumes that contain psoralens. (d) Erythema dyschromicum perstans.
5. ***Drugs*** – (a) Psoralens. (b) Fixed drug eruptions. (c) Arsenic ('raindrop' appearance). (d) Minocycline. (e) Chlorpromazine and other related phenothiazines – slate grey or purple discolouration of skin. (f) Gold and silver occasionally.
6. ***Tumours*** – (a) Acanthosis nigricans (Fig. 57) is characterised by thickening and hyperpigmentation of the skin giving it a typically velvety appearance, often associated with internal malignancy. (b) Metastatic melanoma may produce diffuse slate-blue colour. (c) Mastocytosis.
7. ***Nutritional*** – Pellagra, protein energy malnutrition.
8. ***Familial periorbital hyperpigmentation.***
9. ***Becker's naevus*** affecting young adult males. Pigmented asymptomatic, irregular well demarcated hypertrichotic macule (Fig. 58).
10. ***Freckles*** – Small, circumscribed pale brown macules that appear in sun exposed areas.
11. ***Post-infective*** – in malaria, kala-azar.

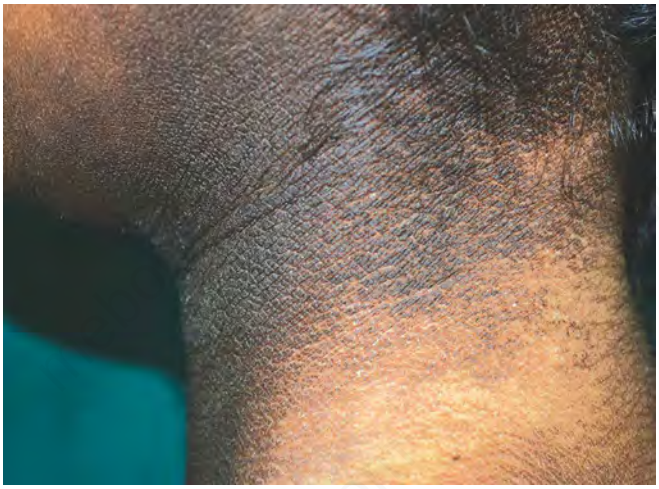


Fig. 57: Acanthosis nigricans

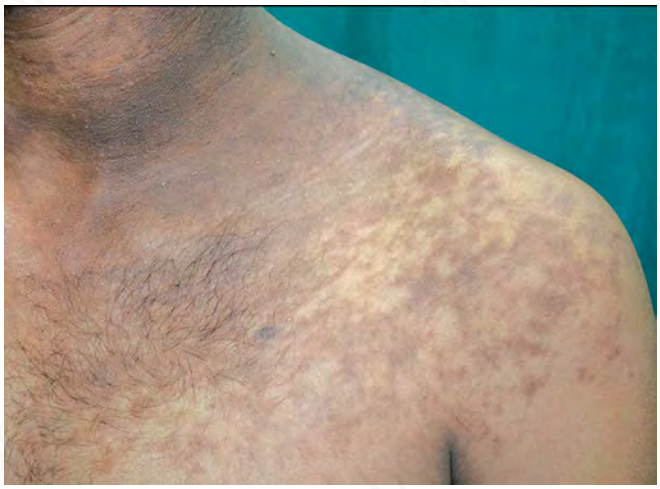


Fig. 58: Becker's nevus

18. DISORDERS OF SWEAT GLANDS

Hyperhidrosis is excessive sweating.

CAUSES

Generalized hyperhidrosis

1. Environmental exposure to heat, exercise.
2. Systemic disorders.
   Infections, e.g. malaria, tuberculosis (night sweats)
   Cardiovascular, e.g. shock, CHF, endocarditis
   Neurological, e.g. Parkinsonism.
3. Endocrine, e.g. hyperthyroidism, diabetes mellitus, Cushing's syndrome, menopause, pheochromocytoma.
4. Neoplasms: Lymphoma, carcinoid syndrome, insulinoma, pheochromocytoma.
5. Drugs and poisons: Antipyretics, emetics, insulin, antidepressants (e.g. fluoxetine), prostigmine. Poisoning with mercury, arsenic, insecticides and herbicides.
6. Nutritional and metabolic disorders: Diabetes mellitus, hypoglycemia, porphyria, obesity, gout, rickets, infantile scurvy, alcoholism, drug withdrawal in drug addicts, pregnancy, menopause.
7. During anxiety, pain and motion sickness or vertigo.

Localized hyperhidrosis or hyperhidrosis of a relatively small area

1. Idiopathic unilateral circumscribed hyperhidrosis
2. Gustatory hyperhidrosis
   - Physiological
   - Pathological: Associated with encephalitis, diabetic neuropathies, Pancoast's syndrome, parotitis or parotid abscess, herpes zoster of preauricular area
3. Emotional: Palms, soles, axillae
4. Associated with glomus tumour, POEMS syndrome, burning feet syndrome, pachydermoperiostosis, pretibial myxoedema, vitiligo, nail-patella syndrome, palmoplantar keratoderma, RA, Raynaud's disease.
5. Brain tumour
6. Injury to spinal cord or nerve

TREATMENT

Systemic – Propantheline bromide 15 mg t.d.s. may be used to treat volar hyperhidrosis. Sedatives and tranquillizers in emotionally labile individuals. In tense and anxious individual psychotherapy and biofeedback.

Topical – is useful for volar axillary forms. For the feet 1% formaldehyde or 10% glutaraldehyde act by blocking sweat spores temporarily. (a) *Aluminium chloride hexahydrate* in anhydrous ethyl alcohol applied at bed time. (b) *Iontophoresis* – Introduction by means of an electric current of ions of soluble salts into tissues of the body for therapeutic purpose. Agents used are tap water, or with anticholinergic drugs, mainly for palmoplantar hyperhidrosis. (c) *Intradermal botulinum toxin* – Type A (BTX-A) is safe and effective for repeated treatment of axillary hyperhidrosis.

Surgical treatment for axillary hyperhidrosis consists of excision of a small area in the axilla where sweat glands are, maximally located. Cervical sympathectomy is tried as a last resort.

HYPOHIDROSIS AND ANHIDROSIS

Causes

Generalized hypohidrosis

I. *Interference with nervous control of sweating*
   1. Brain: Hyperthermia, organic lesions in cortex, hypothalamus, pons and medulla
   2. Spinal cord: Syringomyelia, pansection of cord, tabes
   3. Sympathetic ganglia: Sympathectomy, ganglion blocking drugs
   4. Postganglionic fibers: Congenital insensitivity to pain with anhidrosis, diabetic neuropathy, G-B syndrome, leprosy, alcoholic neuropathy, amyloidosis, gout, Fabry's disease
   5. Anticholinergic drugs

II. *Congenital absence or paucity of sweat glands:* Anhidrotic ectodermal dysplasia, congenital ichthyosiform erythroderma

III. *Atrophy or damage of sweat glands:* Alopecia areata, systemic sclerosis, systemic poisoning (e.g. barbiturates, diazepam)

IV. *Occlusion of pores:* Exfoliative dermatitis, necrosis, and ichthyosis, seborrhoeic dermatitis, tropical anhidrotic asthenia.

V. *Miscellaneous:* Addison's disease, hypothyroidism, uraemia, liver cirrhosis, Sjogren's syndrome, dehydration

Localized Hypohidrosis

I. *Obstruction of duct or pores:* Miliaria, pompholyx, eczemas, papulosquamous eruptions.

II. *Damage to sweat glands:* Inflammation, trauma, tumors, irradiation scars and scleroderma

III. *Congenital absence of sweat glands:* Anhidrotic ectodermal dysplasia

IV. *Local denervation:* Leprosy

V. *Miscellaneous:* Sjogren's syndrome, local radiant heat or pressure

Tr. – Cool surrounding. Avoidance of clothes made of synthetic fibres. For poral occlusion, skin moisturizers.

SWEAT RETENTION SYNDROMES

Miliaria refers to a group of disorders in which there is obstruction to the outflow of sweat through the sweat duct. Types of miliaria:

1. *Miliaria crystallina* (Sudamina) – Discrete or confluent, transparent, thin walled vesicles resembling dew drops, occur on normal skin, often in crops. Lesions are asymptomatic and commonly found in intertriginous areas such as axilla. They soon rupture followed by brawny, superficial desquamation.
2. *Miliaria rubra* (prickly heat) – Small, discrete, erythematous papules or papulovesicles often formed in sheets. Common sites are the neck, flexures and the trunk, particularly under clothing. At times forehead and scalp margins are affected. A pricking or stinging sensation is common and sometimes pruritus.
3. *Miliaria profunda* – Pale, firm papules on trunk and limbs, with insignificant erythema or pruritus.

   Treatment – Cool environment, Avoidance of exercise, and tight clothing. Emollients like lanolin and prickly heat powders. Systemic antibiotics if secondary bacterial infection.

19. SKIN MANIFESTATIONS OF SYSTEMIC DISEASE

LUPUS ERYTHEMATOUS

Lupus erythematous is an autoimmune connective tissue disorder with clinical manifestations ranging from primary cutaneous disorder (discoid LE) to a multisystem involvement with constitutional symptoms (systemic LE). The scales are adherent and the under surface of the scale, if removed shows sharp projections which are keratin plugs that have extended into dilated pilosebaceous openings (carpet track sign, cat's tongue). The plaques expand peripherally with a reversed margin and central depigmentation and atrophy (Fig. 59).

Chronic discoid lupus erythematosus. Lesions comprise well-defined, scaly plaques in which follicular plugging occurs. Chronic lesions show atrophy or scarring, associated with hypo or hyperpigmentation.

Common sites are the face, scalp, forearms and hands. Diagnosis is confirmed histologically, serology is usually negative. *Tr.* – Potent or very potent topical corticosteroid, sun avoidance and the antimalarials hydroxychloroquine and mepacrine. Occasionally systemic corticosteroids, oral gold, dapsone, cyclosporine or methotrexate is used.

Subacute cutaneous lupus erythematosus. Erythematous scaly eruption (which is sometimes annular) on sun-exposed sites (Figs. 60 and 61). Arthritis is a common feature. *Diagnosis*: Skin biopsy and serology. Most patients have antibodies to the extractable nuclear antigen Ro or La. *Tr.* – Topical corticosteroids, sun screen and hydroxyquinolone.

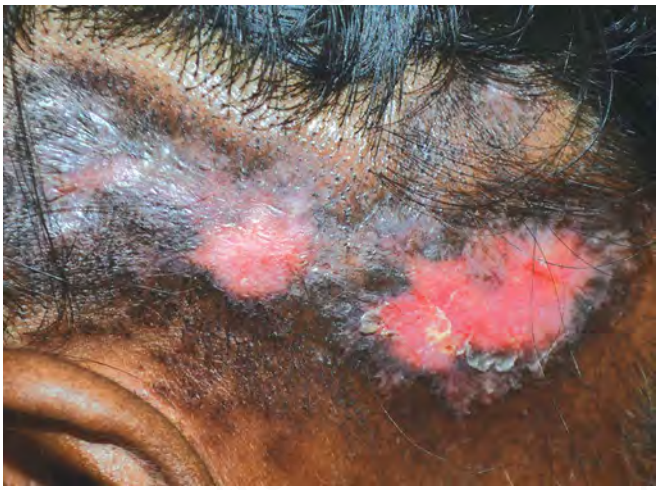


Fig. 59: Discoid lupus erythematosus

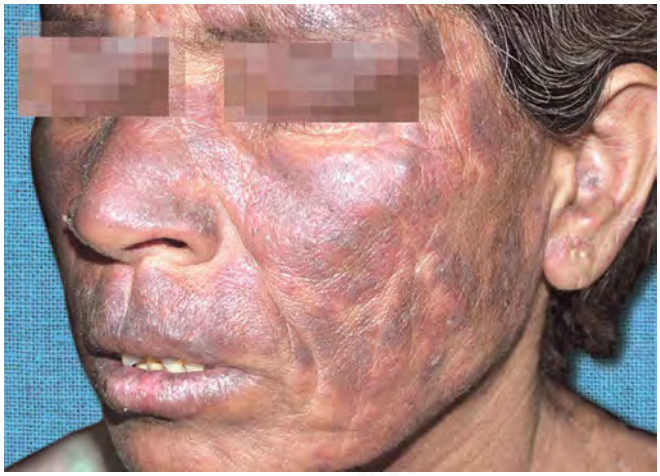


Fig. 60: Subacute cutaneous lupus erythematosus

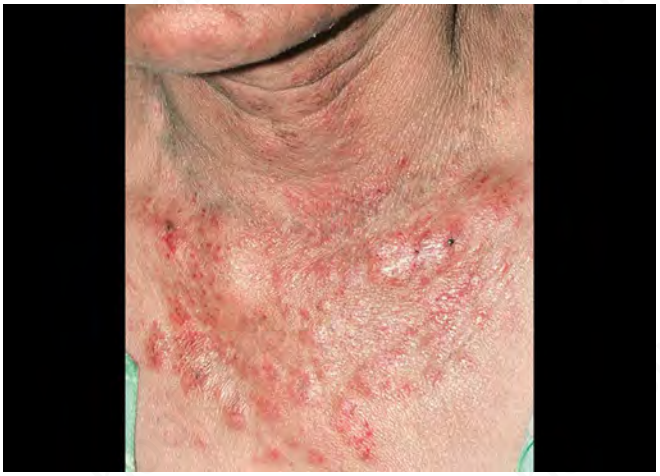


Fig. 61: Subacute cutaneous lupus erythematosus

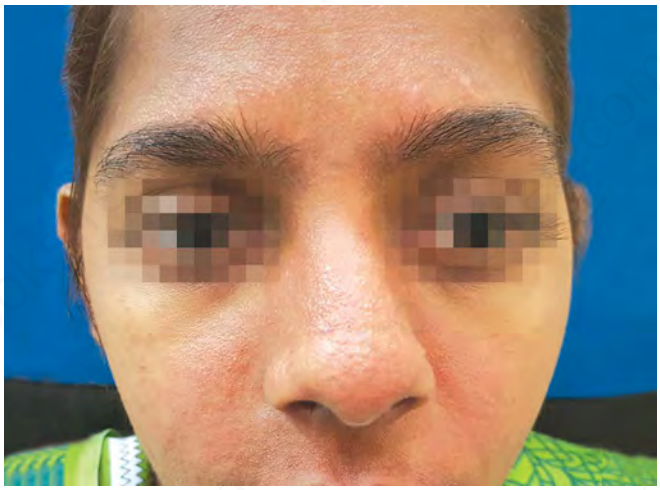


Fig. 62: Malar rash in SLE

Generalized lupus erythematosus (SLE). Typical butterfly rash is seen in about 50% of patients (Fig. 62). They often have nail fold telangiectasia/infarcts, and the rash on the fingers usually affects the interphalangeal skin.

Dermatomyositis usually presents with an eruption affecting the face, neck, shoulders ('shawl sign'), elbows, forearms and hands. The rash tends to be aggravated by sunlight. Pathognomonic features are a violaceous periorbital eruption and scaly eruption over the knuckles (Gottron's papules). *Diagnosis:* Skin biopsy, muscle enzymes, muscle biopsy. Patients with myositis may exhibit the Jo-1 antibody. *Tr.* – Systemic corticosteroids with second-line agents such as methotrexate, cyclophosphamide, etc.

Scleroderma can be subdivided into morphea (localized to the skin) and systemic sclerosis.

MORPHEA

Localized morphea can affect at any age, and female:male ratio is 3:1. Typical lesion is a purple/mauve area of skin. Older lesions become waxy centrally with a lilac coloured edge. Lesions may become hyperpigmented as they resolve, and this can sometimes be the presenting feature. Linear morphea is uncommon. Lesions usually unilateral on the limbs are often cutaneous, but underlying muscle and bone may be involved.

Frontoparietal morphea usually presents as an indurated area on forehead that may spread into the scalp (with associated hair loss) or on to the face.

Generalized morphea is a rare condition in which patients exhibit induration of trunk and proximal limbs. It is sometimes associated with systemic involvement. Serology (antinuclear antibodies and Sc1-70) is usually negative. *Tr.* – Topical corticosteroids may help localized lesions. Systemic corticosteroid, penicillamine, interferon, calcitriol and methotrexate should be used with caution.

Systemic sclerosis usually presents with swelling of the fingers, progressing to typical sclerotic bound-down appearance (Fig. 63), with nail fold infarcts/telangiectasia. Furrowing of the perioral skin with restriction of mouth opening is a characteristic sign.

SARCOIDOSIS

Of patients with systemic disease, 20–30% have skin lesions, but cutaneous sarcoid may present without evidence of systemic involvement. Classically lesions of sarcoid have a violaceous brawny hue and may show 'apple jelly nodules' (granulomata) on compression with a glass

Fig. 63: Hide-bound skin of hands in systemic sclerosis

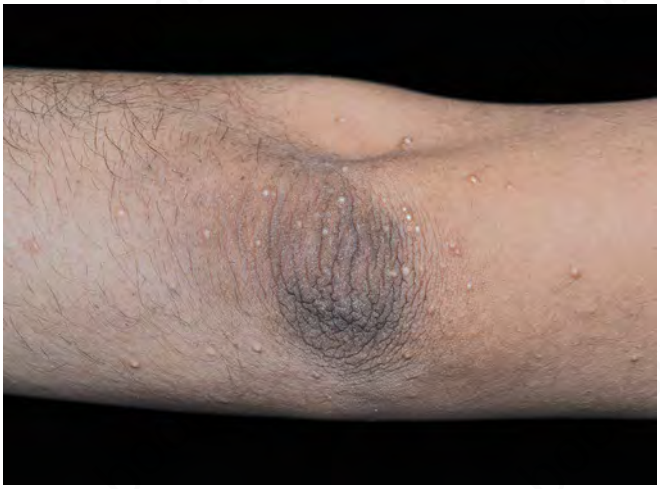


Fig. 64: Xanthomas

slide (diascopy). Lesions of sarcoid do not undergo necrosis, or it is minimal. Most typical lesions are:

Erythema nodosum is most commonly associated with 'benign sarcoid' (bilateral hilar lymphadenopathy and a tendency to spontaneous resolution). Lesions present as painful, red, round nodules of 1–5 cm in diameter on the shins which settle over 2–3 weeks with bed rest and NSAIDs.

Lupus pernio is a pathognomonic change of sarcoid. It presents as violaceous, infiltrated plaques, usually over the nose, ears and nail beds may also be affected. There is usually coexistent chronic fibrotic sarcoid of upper respiratory tract that responds poorly to treatment. Papules, nodules and plaques are seen with general skin involvement. Lesions can be itchy. As the lesions involute, hyperpigmentation remains.

Scar sarcoid. Sarcoid is one of the few conditions that appear in scars (Koebner phenomenon). Its development may signify an exacerbation of systemic disease.

DIABETES

Diabetic dermopathy is the most common dermatosis. It presents as oval, dull-red papules of 0.5–1 cm in diameter that gradually develop to leave a brown atrophic scar. Usual site is the shins. Lesions are thought to be caused by vascular disease.

Necrobiosis lipoidica presents as erythematous plaques on the shins that become yellow and waxy centrally with surface telangiectasia. Only a small proportion of diabetics develop necrobiosis lipoidica but its presents is a strong marker for the disease.

Other skin conditions

- Disseminated granuloma annulare
- Cutaneous infection
- Diabetic bullae
- Acanthosis nigricans (occurs with insulin resistance)
- Cobbled skin over knuckles and finger pulps (finger pebbles)
- Eruptive xanthomata (high serum triglycerides) (Fig. 64)
- Necrolytic migratory erythema with rash (rare)
- Cutaneous skin allergy to hypoglycaemic agents and insulin reactions
- Diabetic foot and diabetic wet gangrene.

MISCELLANEOUS CUTANEOUS SIGNS OF SYSTEMIC DISEASE

Pretibial myxoedema. Waxy plaques on shins with prominent hair follicles ('peau d'orange' appearance). Localized hypertrichosis may occur. It is most commonly associated with Grave's disease. *Tr.* – Topical corticosteroids and octreotide.

Pyoderma gangrenosum. Violaceous nodules, which later ulcerate to produce an ulcer with an overhanging, violaceous edge (Fig. 65). The lesions heal leaving an atrophic/cribriform scar. Underlying causes include inflammatory bowel disease, liver disease and various haematological disorders. *Tr.* – Systemic corticosteroids, cyclosporine and minocycline. Dapsone can also be used.

Acanthosis nigricans has been mentioned earlier.

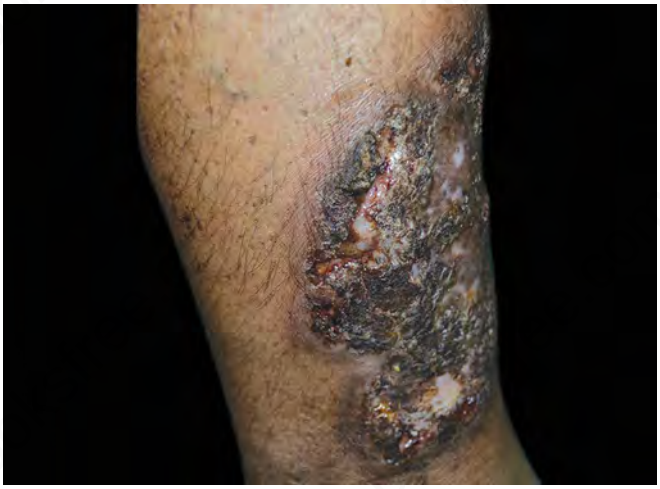


Fig. 65: Pyoderma gangrenosum

Principal types:

- Hereditary benign (autosomal dominant and not associated with endocrine abnormalities).
- Benign (associated with various syndromes in which relative insulin resistance occurs).
- Pseudo (a reversible complication of obesity)
- Malignant (usually secondary to adenocarcinoma)
- Naevoid (usually isolated and localized, and not associated with endocrine abnormalities)
- Severe involvement of palms, mucous membranes or mucocutaneous junctions suggests possibility of underlying malignancy.
- Drug-induced. Drugs that cause acanthosis nigricans such as nicotinic acid, corticosteroids and oral contraceptives.

Tr. – of cause. Locally mild keratolytics like salicylic acid or retinoic acid cream.

Autoimmune disorders (see Chapter 16).

20. GENETIC SKIN DISORDERS

Disorders of keratinization – Keratins are the major structural proteins of the epidermis, and are divided into type I (acidic) and type II (basic). Each is the product of a single gene. Keratin gene expression varies from region to region of the skin, and also between various layers of the epidermis. These explain the variety of clinical manifestations that can follow mutations of keratin genes.

Epidermolysis bullosa simplex and epidermolytic hyperkeratosis. In the former minor friction damages a weakened epidermis and superficial blisters form easily. In epidermolytic hyperkeratosis blistering is a feature in early childhood, but is superseded later by widespread hyperkeratosis.

Palmoplantar keratoderma. Mutations in the keratin genes expressed in palms and soles are responsible for some of the inherited patterns.

Other disorders of keratinization – (a) *White sponge naevus* of the mucosa. (b) *Pachyonychia congenita* – Grossly thickened nails associated with cutaneous hyperkeratosis. (c) *Monilethrix* – Hairs have a curious beaded appearance. (d) *Ichthyosis* – Fish-like appearance of skin. Collagen abnormalities

Dystrophic epidermolysis bullosa. There is easy blistering in response to friction due to weak anchoring fibrils.

Ehlers-Danlos syndrome – Variable degree of joint hypermobility, skin hyperelasticity, poor wound healing and vascular fragility. Mutations occur in a gene encoding lysyl hydroxylase, an enzyme important in the formation of hydroxylysine in collagens.

Disorders of pigment. Neural crest cells migrate out into the skin to become melanocytes. Some genetic pigment disorders are caused by a failure in this migration, others are caused by abnormal pigment production.

Piebaldism. Patchy depigmentation, white forelock, triangle of white skin in the forehead, and a diamond-shaped area on front of the trunk. Piebaldism is inherited as an autosomal dominant trait and is caused by mutations in the *kit* gene on the long arm of chromosome 14. The kit gene encodes a growth factor receptor on certain cells; cells without the receptor fail to respond to normal signals for migration.

Waardenburg syndrome manifests as a white forelock and cochlear deafness. The gene responsible plays an important role in migration of neural crest derivatives.

Albinism. Melanocytes are present in the skin in normal numbers, but little or no melanin is produced. Two genetically distinct types exist: tyrosinase-negative (type I) and tyrosinase-positive (type II). Therefore, children with two albino parents may inherit complementary genes and have normal pigmentation.

COMMON INFLAMMATORY DISORDERS

Psoriasis has a strong genetic component; it sometimes occurs in several generations of the same family and is linked to certain HLA types, notably HLA-CW6 and HLA-DR7. The disorder appears to be polygenic, but an alternative explanation is that psoriasis is not a single disease. For

example, flexural, guttate and pustular variants could have different genetic causes.

Atopic eczema has a complex genetic background.

21. CUTANEOUS ANTHRAX

The word anthrax literally means 'Coal' in Greek. There is a skin lesion of painless black eschar as dark as coal.

Cutaneous anthrax is due to direct contact with contaminated meat, carcasses, hair, hides, wool or bone.

Cl Fs. Cutaneous anthrax accounts for majority of all anthrax infections. Most of the lesions are seen on exposed areas such as face, neck, arms or hands. It usually begins as a painless, itchy papule within 3 to 4 days of inoculation and progresses rapidly into serous or serosanguinous vesicles, which ulcerate with a central black eschar surrounded by a group of vesicles, with marked perilesional oedema, symptoms of toxaemia can occur. The lesion heals within one to three weeks with scarring. Regional lymphadenopathy of submandibular, preauricular and axillary areas and even groins is common.

Diagnosis: A smear from the ulcer shows presence of large, brick-shaped Gram +ve bacilli.

Tr. To avoid bacteraemia, treatment with Penicillin G is advisable.

22. SKIN CANCER

Cancers can arise from any structure in the skin (Table 28).

Malignant melanoma arises from melanocytes in the epidermis.

Aetiology – There is a strong association with exposure to ultraviolet radiation, particularly intense, burning exposure on sunny days. Other risk factors include a first-degree relative with history of malignant melanoma, personal history of malignant melanoma and fair skin type, large congenital melanocytic naevi, or dysplastic naevus syndrome.

Table 28: Derivation of malignant skin tumors

Cell of origin	*Malignancy*
Melanocyte	Malignant melanoma
Epidermal germ cells	Basal cell carcinoma
Epidermal keratinocytes	Squamous cell carcinoma
Endothelial cells	Angiosarcoma
Fibroblasts	Dermatofibrosarcoma
Sweat-duct	Microcystic adnexal
Keratinocytes	Carcinoma

Clinical features. Most common site is lower limbs in women and the back in men. Melanoma can also occur in the eye, juxta cutaneous mucous membrane such as oral cavity, anorectal and vaginal areas. Clinical appearance can vary with type and site of tumour.

Superficial spreading and nodular melanoma. Lesions are asymmetrical with irregular border, contain more than one colour and may be inflamed or crusted.

Lentigo maligna and lentigo maligna melanoma arises on sun-exposed parts of the face in elderly patients. It resembles a large irregular freckle and tends to grow slowly. Malignant transformation into an invasive lentigo maligna melanoma can occur at any time.

Acute lentiginous melanoma occurs on the non-hair-bearing skin of palms and soles, and under the nails (subungual melanoma).

Amelanotic melanoma is often mistaken for squamous cell carcinoma or pyogenic granuloma.

Management. Surgical excision may be curative in thin lesions. Intermediate and thick lesions need lymph node biopsy, further surgery and adjuvant therapy.

Basal cell carcinoma (rodent ulcer) is a common malignancy and is believed to arise from the undifferentiated germ cells of the epidermis. It is locally destructive, but almost never metastasizes.

Aetiology. Sun exposure is the most important factor. Others include exposure to ionizing radiation, arsenic ingestion and rarely, genetic predisposition.

Clinical features. The lesions most commonly occur on exposed parts of face, ears, scalp, shoulders and back, with a particular predilection for the nose (Fig. 66). Clinical appearance can vary according to the site and type of tumour.

Nodulocystic basal cell carcinoma develops as a small translucent, pearly nodule, often with surface telangiectasia. As the lesion enlarges, it often ulcerates to leave an adherent crust and a rolled edge.

Superficial basal cell carcinoma – develops as a pink, scaly plaque that enlarges slowly. In contrast to other forms of basal cell carcinoma, it is commonly found on the trunk and can be confused with patches of eczema, psoriasis or Bowen's disease. If examined in good light, the typical rolled edge and telangiectasis can be seen.

Sclerosing (morphoeic) basal cell carcinoma develops as a slowly expanding, white scar-like plaque with a poorly defined edge, and is therefore difficult to diagnose.

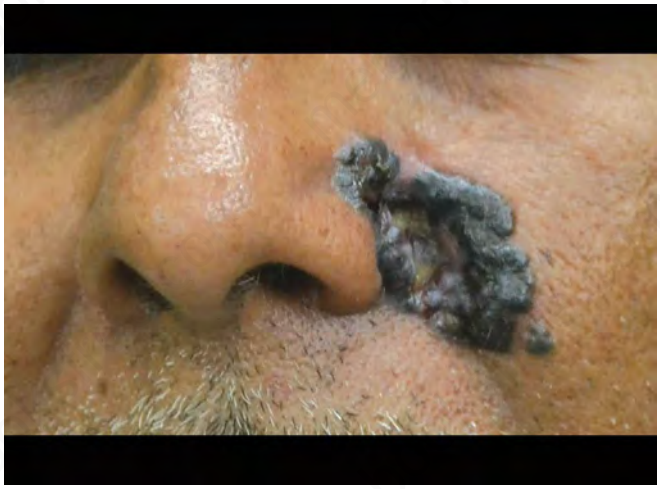


Fig. 66: Pigmented basal cell carcinoma

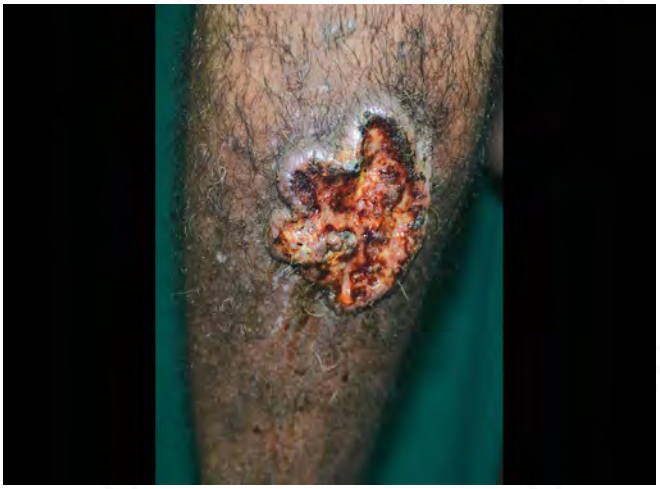


Fig. 67: Squamous cell carcinoma

Management – Aim of treatment is to excise or destroy the entire tumour. Excision is the treatment of choice, though many other techniques (including curettage and cautery, cryotherapy, radiotherapy and micrographic surgery) can be successful.

Squamous cell carcinoma. The spectrum ranges from relatively benign actinic keratosis, through low-grade intra-epidermal carcinoma to invasive squamous cell carcinoma with the potential to metastasize.

Aetiology – The carcinoma usually develops in an area of skin damaged by chronic ultraviolet irradiation. Other factors are chronic ulceration and scarring, exposure to ionizing radiation, contact with industrial carcinogens (e.g. tars, mineral oils), immunosuppression (transplant recipients) and human papillomavirus infection.

Clinical features – Common sites are dorsum of hand, forearm, scalp and lower lip. The lesion begins as a small, crusted papule or plaque which becomes more indurated and nodular and may subsequently ulcerate. Squamous cell carcinoma can also arise in chronic wounds, scars and leg ulcers (Fig. 67). Unexplained deterioration raises possibility of the disease (Marjolin's ulcer).

Management. Surgical excision, radiotherapy can be useful. Cryosurgery and curettage and cautery for early lesions.

Keratoacanthoma is a very rapidly growing tumour which typically begins as a small papule on a sun-exposed site; this grows to form a larger, symmetrical tumour. Untreated lesion resolves spontaneously, but often leaves unsightly scars.

Bowen's disease is squamous cell carcinoma *in situ* (confined to epidermis hair follicles). These low-grade, slow growing lesions seldom progress to invasive squamous cell carcinoma.

Clinical features. A disease of the elderly, it commonly occurs on lower leg (particularly in women), face and neck, as asymptomatic, slowly enlarging, well-demarcated, erythematous scaly plaques.

Management – Good response to topical therapy (5-fluorouracil) and superficial destructive modalities like cautery, curettage, cryotherapy and photodynamic therapy.

Actinic keratosis – presents as small, superficial, scaly lesions in sun-exposed sites. They are relatively benign with a low malignant potential. Treatment is usually reserved for larger, progressive or symptomatic lesions. Actinic keratoses can resolve spontaneously if the involved area is protected from ultraviolet irradiation.

23. BENIGN SKIN TUMORS

Benign skin tumors can arise from any part of the skin (Table 29).

Melanocytic naevi (moles) generally start to appear at puberty and early adult life. A melanocytic naevus often evolves through three stages, from flat, dark, evenly pigmented junctional naevus to a raised, pigmented compound naevus, to a more compound naevus which is flesh-coloured. Some naevi develop a depigmented halo followed by involution of the naevus and repigmentation of the halo (halo naevus).

Atypical melanocytic naevi are so-called because of their irregular outline and large size. Patients with large number

Table 29: Derivation of benign skin tumours

Part of skin	*Benign skin tumour*
Melanocytes	Junctional melanocytic naevus, compound melanocytic naevus, intradermal melanocytic naevus, halo naevus, atypical melanocytic naevus (Fig. 68)
Epidermal keratinocytes	Basal cell papilloma (seborrhoeic keratosis), solar keratosis
Hair follicles	Epidermoid cyst ('pilar cyst')
Fibroblasts in dermis	Dermatofibroma
Blood vessels	Campbell de Morgan spots, spider naevi, pyogenic granuloma

of such naevi may have atypical mole syndrome which is associated with an increased risk of malignant melanoma. *Mn* – Most benign melanocytic naevi do not require excision unless there is doubt about a possible diagnosis of malignant melanoma.

Seborrhoeic keratosis (basal cell papilloma) are common lesions, usually pigmented, and start to appear in the fifth decade in both sexes. The lesions are most common on the trunk and face. Typical lesion resembles a greasy, crusty plaque that is adherent to the skin surface. Many are itchy and get inflamed when scratched. Presence of plugged follicular orifices seen on the surface with a hand lens is a useful diagnostic clue.

Management – Curettage and cautery or liquid nitrogen cryotherapy can be used to remove symptomatic or disfiguring lesions.

Epidermoid cysts are common on the scalp, neck, chest and back, particularly in young adults. They comprise an epidermoid wall surrounding a core containing keratin and its breakdown products. The cyst is situated in the dermis; the overlying skin is usually normal. Epidermoid cysts are usually asymptomatic, but can become inflamed.

Management – Non-inflamed cysts can be excised under local anaesthesia.

Dermatofibromas (histiocytomas) are common, particularly on the lower limbs of women. They are thought to be an abnormal response to insect bite, representing a proliferation of fibroblasts within the dermis. They present as a persistent, firm, hard nodule that is often itchy.

Management – Excision can be done for cosmetic reasons.

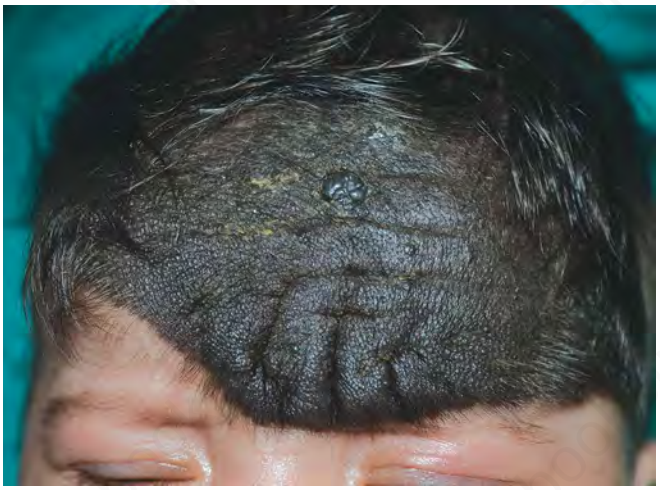


Fig. 68: Congenital melanocytic nevus

Pyogenic granulomas can occur at any age and are typically rapidly enlarging, bright red, juicy lesions that bleed easily. They are most commonly seen on the extremities, and there may be a history of minor penetrating injury earlier.

Management – These lesions are ideally suited for curettage and cautery, but often bleed profusely during the procedure.

24. SKIN PROBLEMS IN TRANSPLANT PATIENTS

INFECTIOUS DISEASES

Viral infections – are generally more prevalent and severe in immunocompromised patients. In renal transplant recipients, this is particularly relevant for human papilloma virus (HPB) associated anogenital cancer and non-Hodgkin's lymphoma, which is associated with EBV infections (simplex and zoster) are a common complication of organ transplantation.

Human herpes virus (HHV8) is now known to be the cause of Kaposi's sarcoma. The condition is most frequent in transplant recipients with high endemic HHV8. It typically presents with violaceous or hyperkeratotic nodules.

Cytomegalovirus (CMV): Cutaneous manifestations are nonspecific. Diagnosis depends on histological findings.

EBV infection is common. Complications include oral hairy leukoplakia and lymphoproliferative disorders.

Bacterial and fungal infections include cellulitis, onychomycosis and other tinea infections.

Skin cancer is one of the most common complications of organ transplantation especially cutaneous squamous cell carcinoma and malignant melanoma.

25. FEVER WITH RASHES

I. Acute illnesses of short duration

1. Exanthema – Measles, rubella, varicella, typhoid, generalized vaccinia, Kaposi's varicelliform eruption.

   Kaposi's varicelliform eruption may manifest as either eczema herpeticum (HIV-1 virus) or eczema vaccinatum (vaccinia virus). Both are complications of atopic dermatitis. Eczema herpeticum is sometimes fatal complication of atopic eczema. Manifested by sudden widespread papulovesicular eruption, often umbilicated, chiefly on areas already affected by atopic eczema with fever and regional lymphadenopathy.
2. Pyogenic – Erysipelas
3. Allergic rashes – Acute allergy – Drug rash, serum sickness, Henoch-Schonlein purpura.
4. Herpes zoster.
5. Rheumatic fever (Erythema marginatum).
6. Infectious mononucleosis – Rash during first week.

II. Subacute or chronic illnesses of long duration

1. Systemic lupus erythematosus.
2. Tuberculosis of skin – Miliary TB, papulonecrotic tuberculide.
3. Erythema nodosum.
4. Lepra reaction.
5. Secondary syphilis.
6. Polyarteritis nodosa.
7. Panniculitis – Commonest form is the nodular, nonsuppurative panniculitis characterized by nodules and plaques of a dusky colour with underlying hard, sclerotic, easily movable masses with relapsing fever and recurrent constitutional symptoms.

III. Rashes or cutaneous diseases complicated by fever

1. Acute dissemination or secondary infection.
2. Pemphigus – Secondary infection.
3. Exfoliative dermatitis – Secondary infection.
4. Scleroderma with secondary infection.

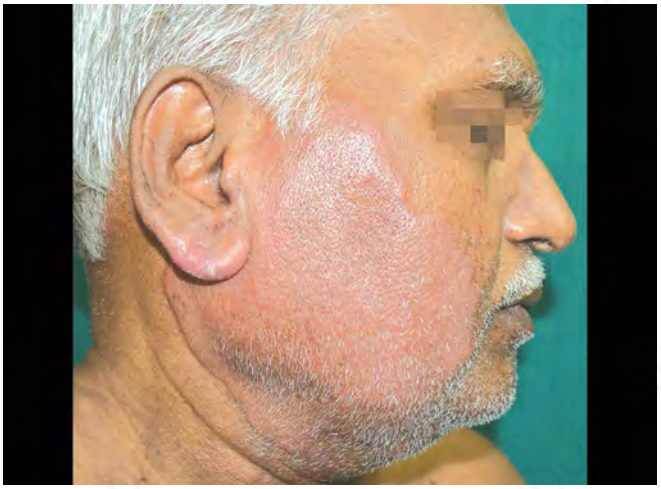


Fig. 69: Borderline tuberculous leprosy with type 1 reaction

5. Leprosy – Lepra reaction (Fig. 69).
6. Papulonecrotic tuberculides.

Addendum (Table 30)

Skin reactions in systemic disease – (Reaction-wise)

1. *Urticaria* – can occur following systemic medication, with infections, e.g. viral hepatitis, with lupus erythematosus, with systemic malignancy.
2. *Erythema multiforme* – Mucocutaneous herpes simplex infection (esp. if recurrent), drug hypersensitivity, infection (esp. mycoplasma pneumoniae and Strepto.), tuberculosis.
3. *Erythema nodosum* –
   - Drugs (sulphonamides, tetracycline, oral contraceptives).
   - Inflammatory bowel disease.
   - Rheumatic disease (including Behcet's).
   - Tuberculosis.
   - Leprosy.
   - Toxoplasmosis.
4. *Generalized pruritus* (Refer).
5. *Erythroderma* – Malignancy (particularly lymphoma).
6. *Purpura* – See blood diseases.
7. *Vasculitis* – Drug hypersensitivity, bacterial sepsis or endocarditis, meningococcemia, rickettsial infections, collagen vascular disease, inflammatory bowel disease, chronic active hepatitis. Henoch-Schonlein purpura in children. Lymphatic leukaemia, Hodgkin's disease (Fig. 70).

Table 30: Cutaneous drug reactions

Toxic erythema	
Penicillins/Cephalo-	Carbamazepine
sporins/Ampicillin	Nalidixic acid
Gentamicin	Phenylbutazone and
Sulphonamides	other pyrazolones
(including thiazide	Phenytoin
diuretics)	
Urticaria	
Salicylates (Aspirin)	Pollen vaccines/vaccines
Penicillins	containing egg proteins
Sulphonamides	Polypeptide hormones
Animal sera	Hydantoin
Phenylbutazone	Toxoids
Yellow dye tartrazine	Cephalosporins
(present in capsule)	Phenytoin
Morphine, codeine	Radiographic contrast media
Fixed drug eruption	
Phenolphthalein	Benzodiazepines
Barbiturates	Paracetamol
Tetracyclines	Quinine
Sulphonamides	Acetylsalicylic acid
Phenylbutazone	Dapsone
Chlordiazepoxide	
Eczematous reactions	
(Other than contact dermatitis)	
Tetracyclines	Isoniazid
Diphenhydramine	Neomycin
Streptomycin	Hydroxyquinolines
Aminophylline	Topical para-amino
Fucidin	products present in
Paraben (preservative in	dyes, sun creams,
medicines) sensitivity	benzocaine.
	Tolbutamide, chlorpropamide.
Erythema multiforme	
(including toxic epidermal necrolysis and Stevens-Johnson syndrome)	
Sulphonamides	Carbamazepine
(and co-trimoxazole)	Organic arsenicals
Phenylbutazone	Rifampicin
Barbiturates	Hydantoin derivatives
Penicillins	

Contd...

Contd...

Photosensitivity	
Tetracyclines (esp.	5 Fluoro-uracil.
chlortetracycline)	Nalidixic acid
Phenothiazines (esp.	Griseofulvin
chlorpromazine)	Amiodarone
Sulphonamides (esp.	
co-trimoxazole)	
Frusemide	
NSAIDs including	
piroxicam	
Pigmentation	
Minocycline	Gold/silver (Blue/grey
Heavy metals	on light-exposed skin)
Carotene	Phenothiazines (bluish
Amiodarone	esp. on face)
Oral contraceptives	Clofazimine (red, brown)
(Melasma)	Phenformin (brown on
Atropine	light exposed skin)
Pilocarpine	Lead poisoning (grey)
Antimalarials (Diffuse	Long-term application of topical hydroquinone (slate grey to blue-black)
grey /brown)	
	Cytotoxic drugs – Busulphan. Bleomycin, Cyclophosphamide (brown)

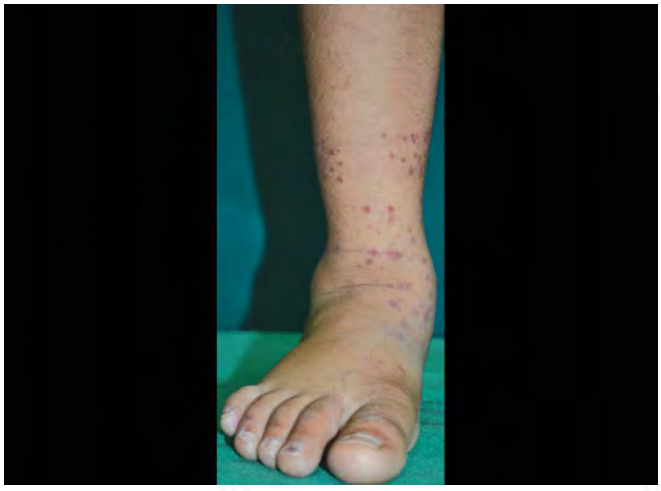


Fig. 70: Leucocytoclastic vasculitis

8. *Pyoderma gangrenosum* – Inflammatory bowel disease, rheumatoid arthritis.
9. *Ichthyosis* (Acquired) – Hodgkin's disease, sarcoidosis, hypothyroidism, internal malignancy, drug reactions.

Systemic disease and the skin (Diseasewise)

1. *Autoimmune diseases* –
   a. Lupus erythematosus
   b. Dermatomyositis
   c. Scleroderma
2. *Haematological/oncological diseases* –
   a. Leukaemia cutis
   b. Lymphomas, e.g. Hodgkin's disease
   c. Multiple myeloma [as cutaneous plasmacytosis, or amyloidosis (Fig. 71)]
   d. Metastatic malignancy
   e. Acanthosis nigricans
3. *Sarcoidosis.*
4. *Endocrine and metabolic diseases*.
   a. Hyperthyroidism – Onycholysis, pretibial myxoedema, dermographism, increased sweating, hair loss, warm, sweaty palms
   b. Hypothyroidism – Myxoedema due to accumulation of mucopolysaccharides, chondroitin sulphate and hyaluronic acid which bind water and lead to a mucinous oedema. The skin is cold and xerotic.
   c. Addison's disease.
   d. Cushing's syndrome.
   e. Gout – Urate crystals in skin.
   f. Hyperlipidemia – Xanthomas.
5. *Gastrointestinal diseases* –
   a. Inflammatory bowel disease.
   b. Dermatitis herpetiformis – in gluten-sensitive enteropathy.
   c. Liver disease – Acute hepatitis, primary biliary cirrhosis.
   d. Malabsorption – Kwashiorkor, acrodermatitis enteropathica (Fig. 72). Livedo reticularis-like hyperpigmentation.
6. *AIDS*
   a. Acute viraemia – Exanthema with red papules.
   b. Nonspecific manifestations – Seborrhoeic dermatitis, extensive skin infections, oral candidiasis, molluscum contagiosum, herpes simplex, warts.

Erythema

1. *Erythema induratum* – Tuberculosis.
2. *Erythema ab igne* – Peripheral neuropathy.
3. *Erythema marginatum* – Rheumatic fever.
4. *Erythema gyratum repens* – Internal malignancy.
5. *Necrolytic migratory erythema* – Glucagonoma.

Central facial rash

1. SLE.
2. Acne rosacea.

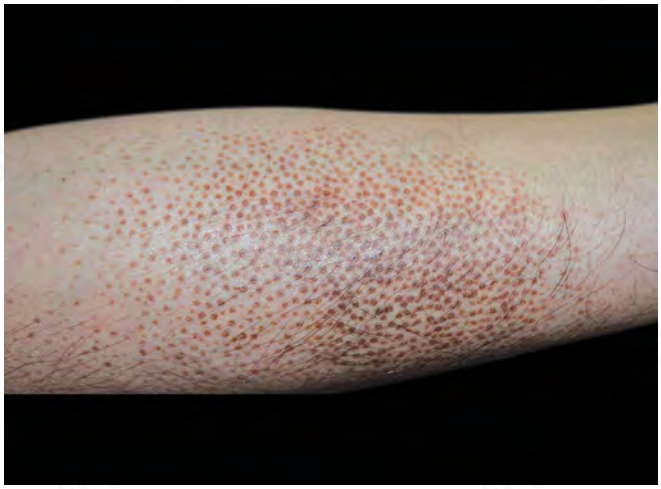


Fig. 71: Lichen amyloidosis

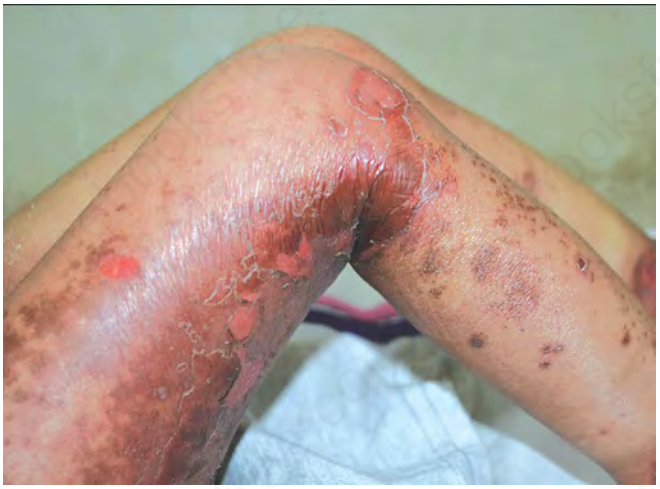


Fig. 72: Acrodermatitis enteropathica

3. Lupus pernio.
4. Dermatomyositis.
5. Porphyria cutanea tarda.
6. Secondary syphilis.

Discrete hypodepigmented areas

1. Tuberculoid and inderminate leprosy.
2. Vitiligo before there is depigmentation.
3. Tinea versicolor.
4. Tuberous sclerosis ('Ash-leaf' macules).
5. Morphea (Localised patches of scleroderma)
6. Naevus depigmentosus is a congenital non hereditary leukodermic.
7. Post-inflammatory.
8. Pityriasis alba.

Conditions predisposing to ampicillin rashes

1. Infectious mononucleosis.
2. CMV infection.
3. Chronic lymphoid leukaemia.
4. Concurrent allopurinol treatment.

Koebner phenomenon

- Psoriasis
- Lichen planus
- Verruca plana
- Vitiligo
- Lichen nitidus

Table 31: Side effects of PUVA treatment

Side effects	*Comments*
Major (long-term)	
Skin cancer	Squamous cell carcinoma
Cataract	UVA screening spectacles must be used during and 24 hrs after exposure
Photodamaging	Damage to dermis results in appearance of ageing and altered elastic properties
Minor (short-term)	
Nausea	
Burning	
Pruritus and Xeroderma	Probably due to psoriasis
Skin disorder caused by UVR	If dose of UVR too high
Psoriasis	Emollients are helpful
Atopic dermatitis	
Acne	Not recommended for patients < 12 yrs.
Mycosis fungoides	
Pityriasis lichenoides	

- Darier's disease
- Molluscum contagiosum

Lasers in dermatology

Treatment of cutaneous vascular lesions

Port wine stains and other ectasia (excluding leg veins) Pulse-dye laser is treatment of choice. Best results are obtained on side of face and forehead

Argon-pumped-dye laser is preferred in treatment of facial telangiectasia because of absence of bruising

Frequency-doubled neodymium: YGA laser is particularly effective in removal of spider naevi and dilated veins on face

Leg vein telangiectasias – Longer wave lengths and pulse durations are required. In many patients sclerotherapy is preferred.

Hair removal – Long-pulsed Nd: YAG laser or Diode lasers can be used

Cutaneous pigmented lesions and tattoos – Epidermal pigmented lesions such as lentigos, freckles and *cafe-au-lait* macules respond well to most of the lasers listed below. More deeply located pigmented lesions require infrared Nd: YAG laser

Q-switched ruby laser

Q-switched Nd: YAG laser

Q-switched alexandrite laser

Resurfacing and ablative lasers can be used for improvement of photodamaged and aged skin. However postoperative pain, swelling and redness can be distressing.

Ichthyosis – The term is derived from 'ichthys' meaning fish and refers to the fish-scale like appearance of the skin.

Classification of hereditary ichthyosis

1. ***Ichthyosis vulgaris*** – Least severe and most common type. Manifests usually after first 3 months of life. Extensor surfaces of extremities more commonly affected. Condition improves as age advances. Keratosis pilaris may be associated.
2. ***X-linked*** – Primarily affects males. Scales larger and darker than ichthyosis vulgaris. Periodic spontaneous shedding of scales may occur.
3. ***Lamellar*** – More severe form of ichthyosis present usually at birth. Death in-utero or shortly after birth. At birth, affected neonates often have a collodion-like membrane over body (collodion babies), membrane is shed soon after birth. Ichthyosis is generalized, palms and soles always affected.

4. ***Epidermolytic hyperkeratosis (EHK)*** usually manifests at birth with tender, raw areas upon which hyperkeratosis develops later. Ridged hyperkeratosis on flexures is characteristic and presence of flaccid bullae is the most characteristic manifestation.

Psoriasis Area and Severity Index (PASI) – The severity of psoriasis is determined by using PASI. The area affected, redness, thickness of plaques and scaling scored for each body zones (head, trunk, arms and legs) and a composite score is derived, ranging from zero (no disease) to 72 (maximum disease).

Tazarotene topical retinoid for psoriasis and acne

Acne – Tazarotene 0.1% gel is applied at night (the surrounding skin being protected by Vaseline) as short contact therapy for 1 to 5 minutes every other night. The drug can be irritating and should be avoided in patients with sensitive skin or seborrheic dermatitis. For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide are significantly more efficacious than all other regimens.

Psoriasis – Tazarotene gel (0.05 or 1%) is an approved topical therapy. However when used as monotherapy, irritation at site of application develops in a significant proportion of patients. When used with mometasone furoate 0.1% cream or fluocinonide 0.05% cream, improvement is enhanced and irritation diminished.

Medical treatment for androgenic alopecia – Androgenic alopecia if not in advanced stage could be treated with Finasteride 1 mg daily for 1–2 years along with Minoxidil 2 to 5% in male subjects.

However Finasteride is contraindicated in liver dysfunction and in patients having low levels of serum testosterone. Also females of child bearing age. Since finasteride is not helpful in postmenopausal androgenic alopecia, the drug of choice is 2–5% minoxidil preparation.

CHAPTER 16

Sexually Transmitted Infections, HIV and AIDS

1. BACTERIAL INFECTIONS

GONORRHOEA

Causative Organism

Neisseria gonorrhoea, is a Gram-negative diplococcus. It infects the mucosal surface of the genital tract, including the urethra in both men and women, the genital glands (Skene's and Bartholin's in women, Cowper's and Tyson's glands in men), the uterine cervix and fallopian tubes, and the epididymides. It can also infect the anal canal and distal rectum, the oropharynx and the eye.

Transmission

Transmission is always sexual in adults, more from males to females. Vertical transmission also occurs. Neonatal sepsis may occur, particularly when there has been prolonged rupture of membranes or preterm delivery.

Clinical Features

Male urethritis – Men with urethral infection develop discharge or discharge with dysuria 3–10 days after exposure, which may vary from scant mucoid to copious and purulent (Fig. 1).

Epididymitis causes unilateral scrotal pain, swelling and tenderness. Rarely there is development of abscesses of Tyson's and Littre's glands or infection of prostate and seminal vesicles.

Cervicitis and urethritis may occur concomitantly. Symptoms include dysuria, frequency and vaginal discharge. The cervix is reddened with mucopurulent or purulent discharge. Pus may be expressed from urethra on pressure against symphisis pubis.

Pelvic inflammatory disease (PID) may occur in some women in the form of salpingitis, pelvic peritonitis and pelvic abscesses, which can give rise to lower abdominal discomfort, marked tenderness on abdominal palpation of adnexa and cervix.

Rectal gonorrhoea usually occurs in homosexual men but can also occur in females who have anal sex. Symptoms are itching, bleeding, purulent discharge, tenesmus and constipation of varying severity. Proctoscopy may show erythema or mucopurulent exudate.

Gonococcal pharyngitis may be asymptomatic or cause sore throat.

Fitz-Hugh Curtis syndrome is gonococcal (or chlamydial) perihepatitis that occurs predominantly in women and gives rise to right upper quadrant abdominal pain, fever, nausea and vomiting.

Diagnosis

Findings of Gram-negative intracellular diplococci on a Gram-stained smear from urethra. In homosexual men, rectal cultures should be obtained if there is history of oro-anal or anogenital contact. The oropharynx should be sampled in all gonorrhoea contacts and in homosexual men. In women, diagnosis is by culture in a selective medium, of a sample from the endocervix. They may have a role in investigation of patients in whom Gram-negative intracellular diplococci are found on microscopy but who are subsequently found to be culture-negative for gonorrhoea.

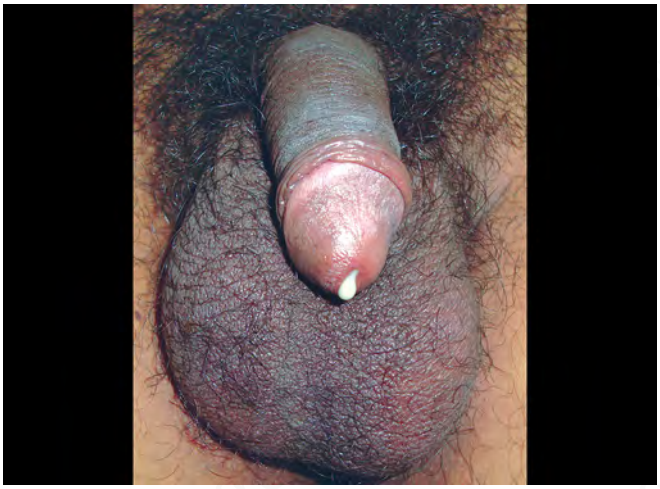


Fig. 1: Frankly purulent urethral discharge in gonococcal urethritis

DISSEMINATED GONOCOCCAL INFECTION

Skin lesions – Commonly on distal extremities, begin as papules or petechiae before evolving into microscopic pustular infarcts. There are seldom more than five or six lesions.

Arthritis is polyarticular arthritis or tenosynovitis, involving knees, small joints of hands, ankles and elbows.

Endocarditis and meningitis are very rare and are most often seen in individuals with a deficiency in one of the components of the complement pathway.

Treatment of uncomplicated genital gonorrhoea – Single dose of Ceftriaxone 125 mg IM or Ciprofloxacin 500 mg. In resistant cases, Spectinomycin 2 g IM. A single oral dose of 2 g Azithromycin is effective against both gonococci and chlamydia.

In men and women with ascending local infection (e.g. epididymoorchitis, salpingitis), standard therapy should be supplemented with a 2-week course of an antichlamydial antibiotic. In pelvic infection metronidazole is added.

CHLAMYDIA AND NONSPECIFIC URETHRITIS

Chlamydia trachomatis is the most common bacterial sexually transmitted micro-organism causing genital and ocular disease. Serovars A-C cause trachoma, serovars D-K affect primarily the genital tract.

Men usually develop urethritis within one month of acquiring infection, but up to 50% are asymptomatic. Occasionally epididymoorchitis develops.

Both men and women develop reactive arthritis (more common in men).

Investigations – Presence of 5 or more polymorphs in urethral smear.

Treatment – Doxycycline 100 mg b.d. for 7 days, or azithromycin 1 g p.o. single dose. In pregnancy and in women who are breast feeding, erythromycin 500 mg b.d. for 14 days or ampicillin 500 mg t.d.s.

NON-GONOCOCCAL URETHRITIS

NGU is inflammation of the urethra with discharge and/or dysuria, but may be asymptomatic.

Aetiology – C. *trachomatis* is the most common cause. Others are *Ureaplasma urealyticum, Mycoplasma genitalium* and *Trichomonas vaginalis.*

Cl. Fs. – Men complain of urethral discharge with or without dysuria or only penile tip irritation. Up to 30% are asymptomatic, but about one-half of these have observable urethral discharge (genitally unaware group). Examination reveals urethral discharge which may be present only on urethral massage. Inflammation of glans and prepuce may be seen.

Circinate balanitis is associated with acquired reactive arthritis, but may occur independent of this.

Investigations – Diagnosis can be confirmed by demonstrating neutrophils in the anterior urethra with a Gram-stained urethral smear or Gram-stained preparation from a first-void urine specimen. A urethral swab should be taken for gonococcal culture and a first-void urine specimen for chlamydial diagnosis. Urinalysis of MSU specimen for using a dipstick can detect leucocyte esterase and nitrites.

Tr. – Same as antibiotics regimen for C. trachomatis.

Bacterial vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of childbearing age. It is a syndrome of unknown cause characterized by depletion of the normal lactobacillus population and overgrowth of vaginal anaerobe, accompanied by loss of usual vaginal acidity.

Cl. Fs. – Offensive, fishy-smelling discharge most noticeable after unprotected intercourse or at the time of menstruation.

Diagnosis – Gram-stain – Examination of a Gram-stained vaginal smear is a quick and relatively simple means of confirming the diagnosis of BV. Its advantages are that it allows recognition of the flora.

Treatment – Metronidazole 400 mg p.o. b.d. for 5 days or 2 g single dose. Topical treatment with intravaginal 2% clindamycin cream or 0.75% metronidazole gel can be used when systemic treatment is not desirable. For relapse – Screening of sex partner for infections. Metronidazole 40 mg b.d. for 3 days starting 2 days before menstruation and again on 5th day of menstruation for 3 months.

SYPHILIS

Syphilis is a chronic STI that is systemic from the beginning and is characterized by florid manifestations and long periods of quiescence. The causative organism is *Treponema pallidum* related to the causative organisms of non-venereal treponematoses. It is also more distantly related to certain saprophytic bacteria found in the mouth and genitalia of healthy individuals.

Both congenital and acquired syphilis are divided into early and late manifestations, usually at 1–2 years after acquisition of infection. The superficial lesions of early syphilis are infectious, those of late syphilis tend to be non-infectious.

Primary Syphilis

Incubation period 9–90 days.

Description – Initial manifestation is a small macule that becomes a papule, which breaks down to form an ulcer (primary chancre). It is solitary, painless with a well-defined margin and an indurated base, and fails to bleed on trauma (Fig. 2). However primary lesions may not have this classic appearance due to secondary bacterial infection, mixed causes or associated HIV infection.

Site – In men the ulcer is found in the coronal sulcus, or on glans penis or penile shaft. In women, on vulva, vaginal walls or the cervix. Usually there is associated bilateral inguinal lymphnode enlargement, discrete and non-tender. In those with cervical chancres inguinal lymphadenopathy is usually absent because lymphatic drainage is to the deep pelvic nodes. Perianal and rectal lesions may occur in homosexual men.

Untreated ulcers resolve spontaneously in 3–8 weeks, usually without leaving a scar.

Secondary Syphilis

Interval between appearance of primary chancre and onset of secondary manifestations is about 6-8 weeks. In about one-third of patients, primary lesions are still evident when secondary manifestations occur.

Clinical features – Onset is characterized by a rash, often accompanied by constitutional symptoms such as fever, headache and malaise.

Rash may be sparse or extensive. Usually nonpruritic.

1. *Macular or roseolar syphilide* – Usually first eruption to appear, lasting only few days. Lesions rose pink in colour, rounded, discrete and chiefly on trunk and flexor aspect of upper limb.
2. *Papular syphilide* – Commonest and most characteristic lesion. Papules dull red in colour, variable in size, rounded, symmetrically distributed; may be covered with scales (Figs 3 to 5). Types of papular rash:
   - *Follicular:* Pointed papular lesions in relation to hair follicles, common on scalp (syphilitic alopecia)
   - *Annular:* Papules arranged in ring form with central clearing, commonly on face
   - *Corymbose lesions* – Large central papules surrounded by small satellite papules
   - Papules in intertriginous areas may become eroded and fissured (split papules). Such lesions occur at angles of mouth, nasolabial folds and behind the ears.
   - *Condylomata lata:* In warm moist areas, papules may become confluent, hypertrophic, pale coloured, broad and flattened. Rarely condylomata lata may involve the face, axillae and neck, or umbilicus, toe webs or eyelids, and can occur alone without any clinical manifestations (Fig. 6).
   - *Rupioid syphilides:* There is extensive tissue necrosis resulting in deeply ulcerated lesions covered with limpet-like crusts.
   - Pustular secondary syphilis may appear as small accuminate pustular syphilide (miliary pustular syphilide), large accuminate pustular syphilide (acne form or varioliform), flat pustular syphilide (impetiginoid or ecthymiform syphilide)

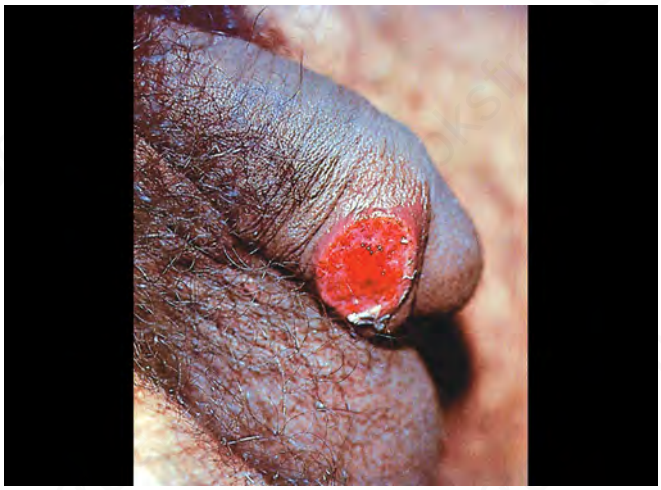


Fig. 2: Primary syphilis: solitary indurated ulcer

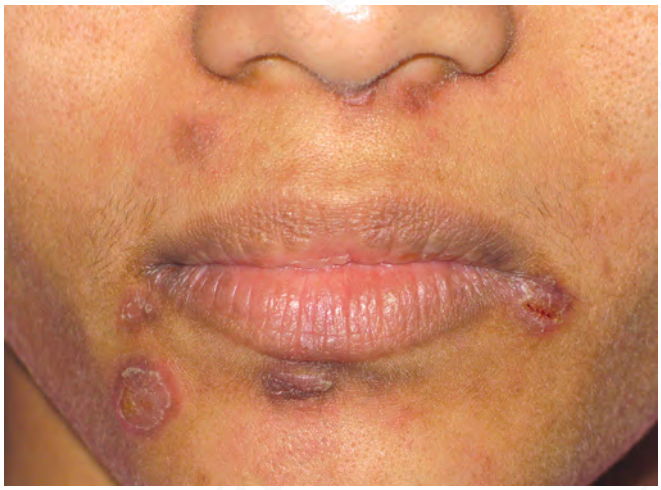


Fig. 3: Secondary syphilis

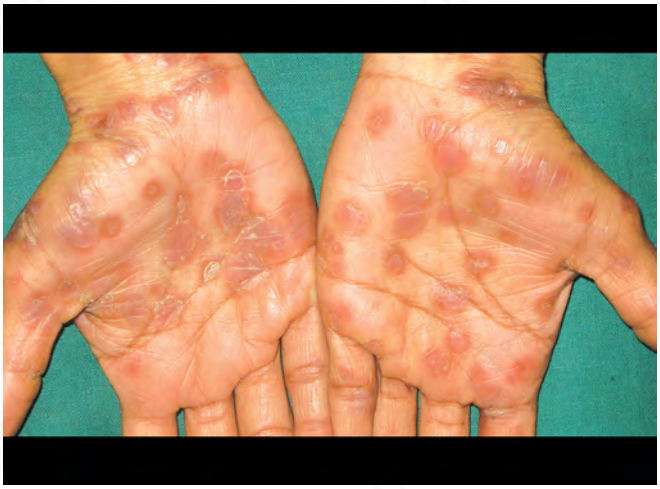


Fig. 4: Secondary syphilis

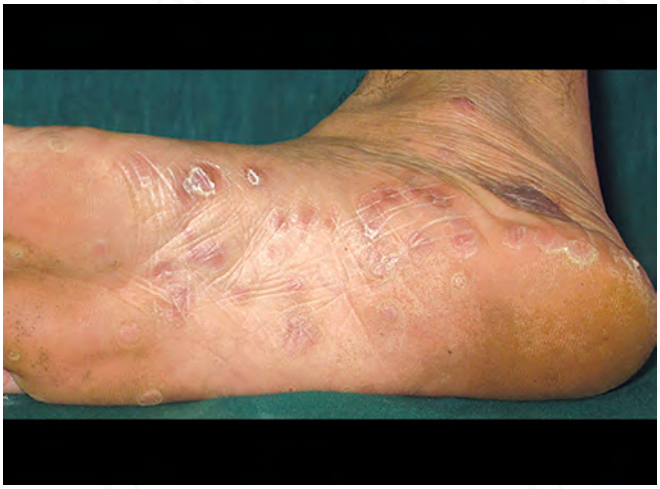


Fig. 5: Secondary syphilis

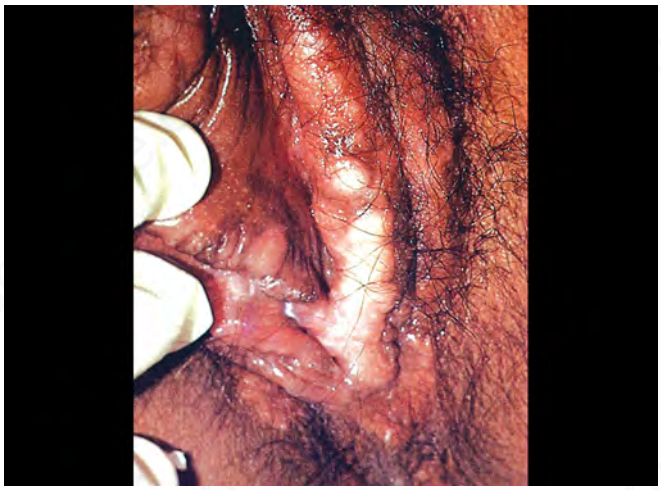


Fig. 6: Condylomata lata: flat papules and plaques, vulva

Regional lymphadenopathy is common. Glands tend to be discrete, rubbery and non-painful. Inguinal, suboccipital and axillary glands may all become involved.

Mucous membrane lesions – Mucous patches may affect oral mucosa, pharynx, larynx and genital mucosa are commonly affected. The patches have a dull red base and greyish slough. Lesions may become confluent with loss of slough, presenting with an erosion with serpiginous outline (snail-track ulcers). Laryngeal lesions involving the vocal cords may give rise to hoarseness of voice. Mucous membrane lesions are painless unless there is secondary infection superadded.

Diagnosis of early syphilis. *T. pallidum* may be detected in primary or secondary lesions using polymerase chain reaction (PCR) analysis.

Early latent syphilis. If secondary syphilis remains undiagnosed and therefore untreated, all visible manifestations of the disease gradually resolve and the patient passes into a stage of no symptoms or signs.

Diagnosis of latent syphilis is based on the results of serological tests and absence of CNS signs and symptoms.

Late Syphilis

Late latent syphilis. By definition, late latent syphilis is also associated with no clinical manifestations, but the time elapsed since acquisition of disease is more than 2 years.

Tertiary syphilis is the destructive stage of the disease. In untreated or inadequately treated patients, signs and symptoms of these late manifestations usually occur after many years after initial infection, and any organ of the body may be involved.

Clinical Features

Cutaneous, mucosal and bony gummas. Gummas are the characteristic granulomatous lesions of tertiary syphilis and usually occur on the skin and mucosal surfaces, and in bone. On healing, nodular skin gummas may leave rounded 'tissue-paper' scars. Mucosal gummas affect the submucous tissues of mouth, throat, palate, larynx, pharynx and nasal septum. They may ulcerate with a 'punched-out' appearance, and the lesions may have a sloughy base. Underlying bony structures may also be destroyed.

Bony gummas are diffuse subperiosteal reactions that often occur in the long bones, particularly anterior margin of tibia. Spontaneous healing results in formation of new bone, and irregular, tender lumps may become palpable.

Formation of lytic lesions may lead to perforation of hard palate or nasal septum, resulting in collapse of the nasal bridge. The skull may also be affected, with a 'worm eaten' appearance on radiography.

Cardiovascular syphilis. Main feature is aortitis, which may be complicated by coronary ostial stenosis, aneurysm and aortic incompetence.

Neurosyphilis may be asymptomatic or manifest as meningovascular syphilis, tabes dorsalis or GPI.

Diagnosis of tertiary syphilis is on clinical grounds and CSF. Findings of 5 or more lymphocytes/μL, excess globulin and serological tests for syphilis are required.

Investigations

1. Demonstration of *T. pallidum* from lesions. (a) Dark ground microscopy. (b) Direct fluorescent staining method.
2. Serological tests

   Reagin tests. VDRL and the rapid plasma reagin (RPR) are sensitive simple and inexpensive and are used for screening but are not specific for syphilis. Results may be presented qualitatively (e.g. reactive, borderline, non-reactive).

   Treponemal tests detect antitreptonemal antibodies. The tests include fluorescent treponemal antibody absorption test (PTA-ABS tests), microhemagglutination assay for antibodies. *T. pallidum* (MHA-TP) and *T. pallidum* haemagglutination assay (TPHA). Treponemal tests are very sensitive for syphilis, neither of the above tests become positive until 3 to 6 weeks after the initial infection.

Quantitative reagin tests may also be used to assess efficacy of therapy. After successful treatment of early syphilis, the titre should decrease and eventually become negative. However, positive antibody titres may persist following treatment of late stages of the disease.

Monitoring Response to Treatment

- All patients should undergo RPR or VDRL testing each time they present with a new episode of an STI.
- On receipt of all tests, results (including titres) should be noted.
- Depending on the initial clinical presentation, patients with a positive RPR test should be treated for early or late syphilis (single or three weekly injections of benzathine penicillin). Patients with no clinical signs of disease should be presumed to have latent syphilis and should be treated with three weekly injections.
- Follow-up after 3 months when RPR/VDRL serology is done. If titre remains the same or decreases further no treatment should be given. If it increases, patient should be treated, but for early syphilis only (i.e. single injection of benzathine penicillin 2.4 MU).

Note: There are no serology tests or combination of tests that can be performed on a single serum specimen to indicate whether patient has active disease or is free of disease.

Treatment of Syphilis

Primary, secondary and early latent syphilis

- Benzathine penicillin G. 2.4 MU i.m. usually into two sites (4 mL into each buttock) at a single visit. Additional doses 2.4 MU should be given 7–14 days later for latent syphilis of unknown duration because of occasional treponemal persistence in CSF after single dose regime.

  In patients allergic to penicillin – Ceftriaxone 125mg IM od × 10 days, azithromycin 1g po, od or doxycycline 100 mg bd × 14 days.

Late or Tertiary syphilis

Post treatment follow up – Examinations and reaginic tests should be performed at 3, 6 and 12 months after treatment and annually thereafter until non-reactive. Failure to decline by 4 fold at 6 months suggests treatment failure and indicates need for retreatment.

Neurosyphilis or ocular syphilis

Aqueous penicillin 12–24 MU/day (2–4 MU every 4 hours) i.v. for 10 days, followed by benzathine penicillin G, 2.4 MU i.m. weekly for 3 weeks or

Aqueous procaine penicillin G, 2.4 MU daily i.m., plus probenecid. 500 mg q.d.s., both for 10 days, followed by benzathine penicillin G, 2.4 MU I.M. weekly for 3 weeks.

Syphilis and Concurrent HIV Infection

Unusual manifestations

- Increased severity of clinical manifestations
- Rapid progress of syphilis to tertiary stage after initial infection
- Relapse in spite of therapy
- Infection not controlled by Benzathine penicillin therapy
- Unusual features like unusual gummatous lesions

Congenital syphilis – See Diseases of Children.

VIRAL INFECTIONS

Genital Warts and Genital Papillomavirus Disease

Genital warts (Fig. 7) are usually caused by human papilloma virus (HPV) types 6 and 11. However, a wider spectrum of HPV types can infect the genital mucosa. HPV virions are small, non-enveloped capsids enclosing on 8 kb circular dsDNA genome. HPV is exclusively epitheliotropic and infects either cutaneous or mucosal epithelium.

Clinical Features

Anogenital warts refer to macular, papular or pedunculated lesions of anal/and or genital mucosa and its adjoining areas. Occur in males on the frenulum, corona, glans, urinary meatus, shaft of penis, scrotum, groin, perineum and perianal areas. In females they occur in the vaginal introitus, fourchette, labia minora, vagina, cervix, perineum and perianal area (Fig. 8). In both sexes, proctoscopy may reveal lesions in the anal canal as far as the dentate line.

Bowenoid papulosis is an HIV-16-induced disease of male and female external genitalia, with itchy, pigmented papules with high degree of intraepithelial neoplasia. In women, these may be associated with multifocal genital tract precancer involving cervix, vagina, vulva or anus.

Buschke-Lowenstein tumors (Giant condylomata) are uncommon, locally aggressive, non-metastasizing verrucous carcinomas. They contain HPV-6 or HPV-11.

Cervix – Colonoscopy shows a spectrum of change from condylomata to cervical intra-epithelial neoplasia (CIN).

Warts in oral cavity are seen occasionally and are associated with orogenital contact.

Diagnosis (a) *Aceto-whitening* – Application of 5% acetic acid to the external genitalia in men or women, or to the cervix can disclose previously unidentified subclinical HPV lesions. (b) *Colposcopy* shows changes of condylomata to cervical endothelium neoplasia. It is useful for taking biopsy. (c) *Cervical cytology* when warts or a macroscopic abnormality is seen on cervix during speculum examination. (d) *Biopsy* – Excision or punch biopsy on external genital lesions in whom there is suspicion of intra-epithelial neoplasia. (e) *STI screening* – Up to 20% of patients with genital warts have another STI.

Management

1. ***Podophyllin*** 20–25% solution is painted on individual lesions in the clinic, allowed to dry and washed carefully off after 4 hours. One or two applications per week until warts have disappeared. There are reservations about podophyllin treatment – it is non-standardized, contains mutagens, and serious side effects (including neurotoxicity and foetal death, usually associated with use of large volumes) have been reported.
2. ***Trichloracetic acid*** (TCA) 90–99% solution, is useful for small discrete lesions. It is applied directly and sparingly with an orange stick or fine swab. The treated areas are bathed twice daily and assessed after 7 days. Repeated use can cause scarring.
3. ***Cryotherapy*** is useful for keratinized, recurrent, large or meatal lesions. It can be administered by closed cryotherapy systems using nitrous oxide or liquid nitrogen, by direct application of liquid nitrogen. Treatment can be given weekly.
4. ***CO_2 laser.***

Fig. 7: Condyloma acuminata

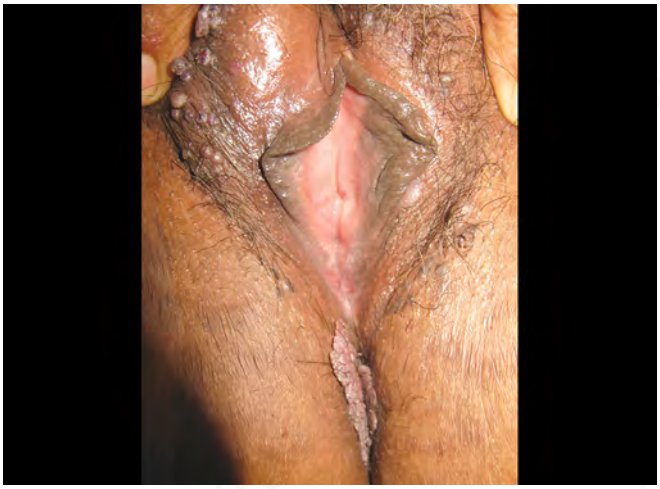


Fig. 8: Genital warts

5. ***Intralesional bleomycin***, a cytotoxic drug that inhibits DNA synthesis.
6. ***Imiquimod*** is an immunomodulator available as 5% cream for self-treatment of external anogenital warts. It acts by causing macrophages to release interferon-α and cytokines, which seem to induce an immune response. It must be applied for 3 nights per week for 6-12 weeks.
7. ***Surgical treatments*** include curettage (intrameatal or labia minora warts), electrosurgery under local anaesthesia (keratinized lesions), scissor excision under general anaesthesia (multiple, large genital warts). Laser surgery is an alternative therapy only for large or recalcitrant warts.
8. ***HPV vaccine*** – A quadrivalent recombinant vaccine for prevention of HPV associated genital diseases in females 9 and 26 years in 3 doses at 0, 2 and 6 months.

GENITAL HERPES

Genital herpes simplex virus is the most common cause of genital ulceration and leads to local, systemic and psychosexual complications. Following initial infection, replication of HSV at the portal of entry results in infection of sensory nerve endings. Viral nucleocapsids are then transported by retrograde axonal flow to the neuronal cell nuclei within sensory ganglia where latency is established.

Transmission

Can occur through genital-genital and oro-genital contact. Infectivity is increased during prodromes and immediately after the lesion heals.

Factors which affect transmission – (a) Infection is more easily passed from males to females. (b) Risk of infection is reduced by about two-thirds when the partner has previously been infected with a different HSV type. (c) There is little risk of reinfection when the partner has already been infected with the same viral type. (d) HSV infection in either partner facilitates transmission of HIV infection.

Neonatal herpes – During pregnancy exposure to virus occurs during passage through an infected birth canal.

Clinical Features

Incubation period is 2–14 days and the average untreated attack lasts 22–28 days.

Description – Initially erythematous papules form in which the characteristic herpetic vesicles erupt. By the time the patient presents, they have usually ruptured, with resulting ulceration. Ulcers are superficial with erythematous outline and greyish base, and are very painful. Lesions tend to be bilateral, and painful inguinal lymphadenopathy is present. Symptoms are more severe in women and in homosexual men (Figs 9 and 10).

Complications – (a) *Local* – Superinfection with fungi and bacteria. Labial and vaginal adhesions may occur, and uncircumscribed men may develop phimosis. (b) *Systemic* – Involvement of pharynx, meningeal irritation. Autonomic dysfunction is rare, it results in difficulty in urinating, constipation and altered sensation in perineal, sacral and lower back areas. Transverse myelitis is another rare complication.

HSV is one of the most common causes of erythema multiforme.

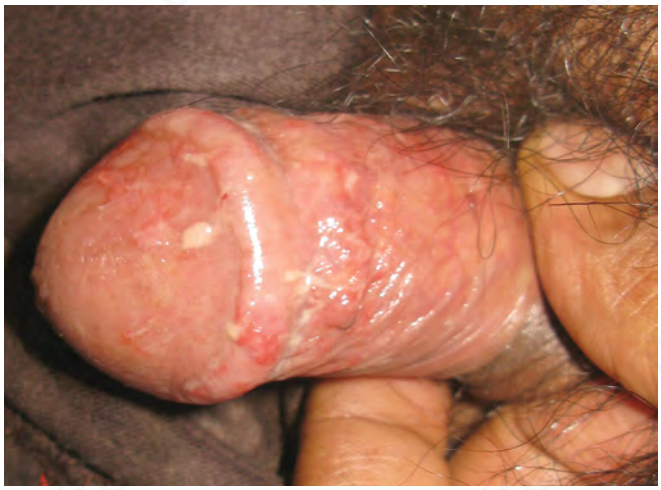


Fig. 9: Herpes genitalis

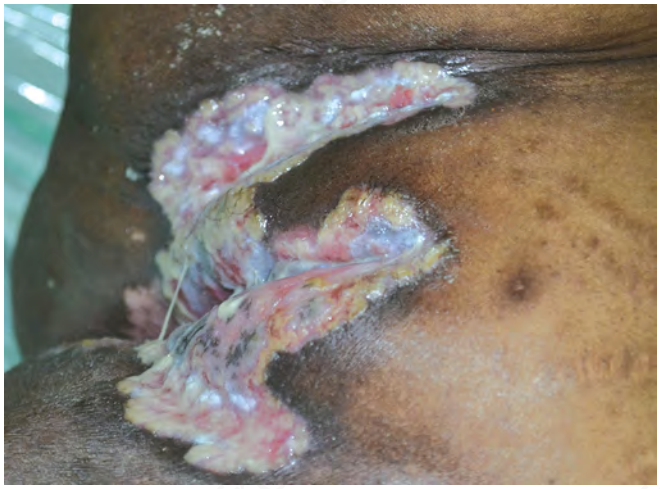


Fig. 10: Herpes genitalis

Recurrent Herpes

Recurrent attacks are usually milder and of shorter duration (up to 8–12 days). Women are affected more severely. Lesions appear in localized sites and are usually unilateral, with only few vesicles. Symptoms in prodromal phase vary from mild tingling sensations in areas affected by the eruption, to severe shooting pains in thigh, buttocks or groin. Other features are malaise, fever and hyperaesthesia at the site where lesions subsequently occur.

Many patients suffer 'atypical' recurrent attacks in which vesicles and ulcers do not occur and fissuring, furuncles, excoriations and nonspecific erythema may be seen.

Genital recurrences are most common in those infected with HSV-2, particularly in the months immediately after initial infection. The fear of disease transmission and severity of recurrent illness can cause psychosexual morbidity.

Investigations

(a) Track smear is useful for rapid diagnosis and is done by scraping base of a ruptured vesicle and staining with Giemsa or Wright stain, multinuclear giant cells are diagnostic on immunofluorescence. (b) Histopathology – Ballooning of epidermal keratinocytes and formation of multinucleate intraepidermal vesicles. (c) Viral culture is a definite diagnostic test for acute HSV infection. (d) HSV direct detection tests include cytology, electron microscopy, HSV antigen detection, HSV-DNA detection. HSV-PCR a highly sensitive detection method is likely to replace viral culture for diagnosis of genital herpes in patients with active mucocutaneous lesions. (e) Enzyme immunoassay (ESA) is used for direct detection of HSV antigen.

Serology – for detecting antibodies to HSV in blood include ELISA, complement fixation test (CFT) and western block.

Management

Antiviral agents for treatment of genital herpes

See Table 1.

Table 1: Antiviral agents for treatment of genital herpes

Drug	*Dosage*	*Side effects*
Acyclovir	400 mg po tds × 7–10 days	Nausea, vomiting, headache, diarrhoea, dizziness, rash
Famciclovir	250 mg 5 times/d × 7–10 days	Fatigue, headache, nausea, pruritus
Valacyclovir	1 g po × 7–10 days	Headache, nausea, dizziness, vomiting

Treatment

Severe disease complications – e.g. pneumonitis, disseminated infection, hepatitis, meningitis or encephalitis. *Tr.* (a) Hospitalization. (b) Acyclovir – 5–10 mg/kg body wt. IV q8h for 2–7 days or until clinical improvement followed by oral therapy for 10 days.

Recurrent genital herpes – (a) Episodic treatment – Antiviral drug for 5 days given early reduces duration and severity of recurrence (b) Suppressive treatment – Daily acyclovir is effective in controlling recurrence, however many patients experience breakthrough attacks while taking treatment.

TRICHOMONIASIS

Trichomoniasis is a common STI caused by *Trichomonas vaginalis,* a flagellated protozoan.

Transmission is by sexual contact. Also from infected mothers to female babies. Predisposing factors include non-use of condoms, or oral contraceptives, smoking and low socioeconomic status.

Trichomoniasis, like many other STIs, can act as a co-factor for HIV transmission. This is thought to occur through increased local accumulation of HIV-infected or HIV-susceptible immune cells.

Table 2: Differentiation of common sexually transmitted genital ulcers or nodules

Disease	*Features*
Syphilitic chancre	Solitary ulcer, indurated, rubbery and slightly tender. Non-tender adenopathy
Herpes simplex	Clusters of small, superficial ulcers on an erythematous base, painful sometimes with vesicles. Inguinal adenopathy.
Chancroid	Shallow ulcer, non-indurated, painful, ragged undermined edges. Ulcers vary in size and often coalesce. Buboes.
Lymphogranuloma venereum	Small papule or ulcer often asymptomatic is very tender and painful buboes with distal lymphedema or drainage to the skin
Granuloma inguinale	Elevated, velvety, granulomatous lesions. No inguinal adenopathy
Primary HIV infection	Multiple, shallow lesions. Systemic symptoms like fever, rash, adenopathy
Scabies (excoriated)	Multiple shallow lesions. In scabies characteristic extragenital lesions and mite burrows.
Pediculosis pubis	Presence of lice

Clinical Features

In women – Vaginitis and vulvitis. Vaginal discharge is green, frothy, itchy and malodourous. Vaginal walls may be erythematous and a 'strawberry cervix' may be seen. Symptoms may worsen during or shortly after menstruation.

In men – *T. vaginalis* may infect the urethra, epididymis and prostate gland. Most men remain asymptomatic. Others present with nonspecific urethritis, rarely balanoposthitis, epididymitis or prostatitis.

Diagnosis – (a) Microscopic examination of saline wet mounts taken from posterior vaginal fornix or urethra to demonstrate motile *T. vaginalis.* (b) Broth culture methods. Disadvantage is the need to incubate samples for several days.

Management – Metronidazole 2 g p.o. single dose or 400 mg b.d. for 5–7 days. For resistant cases – Metronidazole i.v. or higher dose p.o. combined with metronidazole vaginal pessaries. Alternative therapies are vaginal tinidazole, clotrimazole or acetarsol pessaries, vaginal paromomycin preparations and combinations of broad spectrum antibiotics and metronidazole.

GENITAL CANDIDOSIS

Strains of *Candida albicans* constitute 90% of yeasts isolated from the vagina. Candida is the second most common vaginal infection.

Asymptomatic candidosis is common and factors associated are:

- Pregnancy
- Uncontrolled diabetes mellitus
- High oestrogen oral contraceptives
- Corticosteroid therapy
- Antimicrobial therapy (oral, parenteral or topical)
- Use of IUD
- Immunosuppression
- High frequency of coitus (vaginitis only)

Clinical Features

- Vulval pruritus is the most common symptom.
- Vaginal discharge is often minimal. Described as being typically cottage cheese like, it may vary from watery to homogenous thick.
- Vaginal soreness, irritation, vulval burning, dyspareunia and external dysuria are common.
- Odour is minimal and inoffensive.
- Examination reveals erythema and swelling of labia and vulva, often with distinct peripheral lesions.

Diagnosis

(a) Microscopic examination of vaginal secretions. (b) pH – is normal (4–4.5). If > 4.5 possibility of bacterial vaginosis, trichomoniasis or mixed infection. (c) Vaginal cultures in suspicious cases with negative microscopy.

Management

Topical antimycotic agents –are available as creams, lotions, vaginal tablets, suppositories and aerosol sprays. Nystatin cream and vaginal suppositories achieve cure rate of about 75%. Azole derivatives (clotrimazole, miconazole, econazole, luliconazole) are successful in up to 90% cases.

Oral antimycotic agents – Ketoconazole 400 mg/day for 5 days, itraconazole 200 mg/day for 3 days or 400 mg for 1 day, and fluconazole 150mg single daily dose, achieve cure in acute candidal vaginitis. For recurrent cases suppressive prophylaxis with ketoconazole 100 mg/day for 6 months, or weekly fluconazole 100 mg, or topical clotrimazole 500 mg.

Balanitis/Balanoposthitis

Two forms are associated with *Candida* spp. and are acquired sexually.

Superficial but invasive infection occurs particularly in diabetic and uncircumscribed males. It is characterized by intense pruritus, discomfort, erythema and swelling localized primarily to the glans, but may extend to involve the penile shaft and scrotum.

Tr. – Topical antimycotics or systemic azoles.

A milder but more common and particularly recurrent form in which penile cultures may be negative for Candida. Symptoms of local erythema or rash and pruritus appear soon after unprotected intercourse, are transient and relieved by washing or topical corticosteroids.

Scabies and Crab lice have already been described.

TROPICAL STI

Genital ulceration is recognized as a significant risk factor for acquisition and transmission of HIV among heterosexuals in developing countries.

CHANCROID (SOFT SORE)

Chancroid is an STI causing painful genital sores and inguinal lymphadenopathy that may progress to abscess (bubo) formation. Causative organism is a Gram-negative bacterium *Haemophilus ducreyi.*

Pathogenesis – Abrasions are necessary for *H. ducreyi* to penetrate the epidermis and cause infection. The organisms are found in macrophages and neutrophils, and free in the interstitium.

Incubation period 4–7 days.

Description – Lesions start as a tender papule that develops into pustule, then an ulcer. The classical ulcer has a ragged, undermined edge with a grey or yellow base that bleeds when touched. Lesions may be single or multiple (Fig. 11).

Sites – Prepuce, coronal sulcus, frenum and glans in men, and the labia minora and fourchette in women. Ulcers of vaginal wall and cervix may occur. Extragenital lesions are rare.

Lymphadenopathy – Unilateral or bilateral enlargement of inguinal lymph glands is common. Bubo formation may require aspiration. HIV-infected individuals may develop extensive genital ulceration.

Sequelae

- Phimosis or paraphimosis
- Phagedenic ulceration
- Urethral fistulas

Bubos that rupture may take long to heal.

Clinical Variants

- *Giant chancroid* – Large ulcer due to extension of single ulcer or autoinoculation.
- *Phagedenic ulcer* – Large, destructive ulcer with necrosis of tissue from secondary infection.
- *Papular chancroid* begins as an ulcer but later becomes raised around its edges.
- *Transient chancroid* – Small ulcer that resolves spontaneously in a few days. It may be followed by acute regional lymphadenitis.
- *Follicular chancroid* – Originates in the follicles and may be seen on vulva and on hairy areas of genitals.
- *Granulomatous ulcer* resembles granuloma inguinale

Diagnosis – (1) *Smear* – Gram stain material from ulcers may show Gram-negative coccobacilli in a 'school of fish' or 'railroad track' appearance. (2) *Culture* – Sensitivity is only about 75% and requires more than one culture media.

Non-culture diagnostic tests – (a) DNA amplification technique. *Polymerase chain reaction* (PCR) tests are the most sensitive method. Serological tests are unable to differentiate between old and new infections. (b) Antigen detection using immunofluorescence techniques on smears from genital ulcers and bubo aspirates. (c) Mass spectrometric methods can rapidly identify *H. ducreyi.* (d) *Histology* – Superficial necrosis with large number of neutrophils, endothelial proliferation and infiltration with plasma cells, lymphocytes and fibroblasts.

Treatment – Azithromycin 1g orally as single dose or Ciprofloxacin 500 mg b.d. for 3 days, erythromycin 500 mg q.d.s. for 7 days (in pregnant women), or ceftriaxone 250 mg i.m. stat. Healing of ulcers is usually after 7–14 days.

DONOVANOSIS (GRANULOMA INGUINALE)

Donovanosis is a chronic progressive bacterial infection that usually involves the genital region. Causative organism is *Calymmatobacterium granulomatis* (Klebsiella granulomatis).

Incubation period is about 50 days.

Transmission – Sexually transmitted.

Description – The classical lesion (granulomatous) is a beefy red ulcer that bleeds readily on touch (Fig. 12). The lesion enlarges by contiguous spread and gradual peripheral extension. Contact infection occurs between the skin of scrotum and thigh.

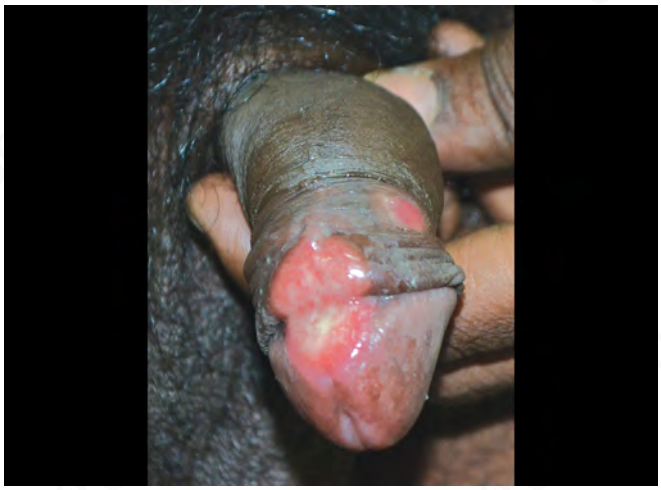


Fig. 11: Chancroid

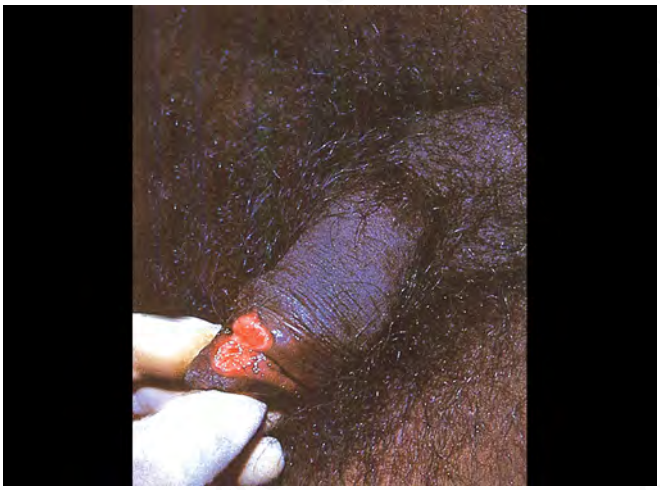


Fig. 12: Donovanosis: clean shiny beefy red lesions with a pearly border

Site – Common sites are prepuce, coronal sulcus, frenum and glans in men and labia majora and fourchette in women.

Extragenital lesions may rarely involve lips, gums, cheek, palate, pharynx, larynx and chest.

Haematogenous spread to liver and bone can occur.

Inguinal lymphadenopathy is uncommon unless there is secondary infection.

A subcutaneous granuloma in inguinal region (pseudobubo) may be mistaken for inguinal lymphadenopathy.

Sequelae – Stenosis of urethra, vagina or anus, elephantoid enlargement of external genitalia and possibly carcinoma.

Diagnosis – (a) *Microscopic identification* of Donovan bodies, in tissue smears using Giemsa or Wright's stain. Donovan bodies can be seen in large mononuclear cells as Gram-negative intracytoplasmic cysts filled with deeply-staining bodies which may have a safety-pin appearance. (b) *Histological changes* include chronic inflammation with infiltration of plasma cells and neutrophils. Epithelial changes include ulceration, microabscesses and elongation of the rete ridges. (c) *Culture* of the organism has been reported in peripheral blood monocytes and in Hep-2 cells. (d) *PCR analysis* using a colorimetric detection system can be used. (e) *Tests for concomitant STDs*.

Tr. – Doxycycline 100 mg po bd or Ciprofloxacin 750 mg bd or Trimethoprim sulphamethoxazole (80/160 mg) tablet bd for 14 days. All for 3 weeks till all lesions have completely healed.

LYMPHOGRANULOMA VENEREUM (INGUINAL BUBO)

LGV is an STI caused by *Chlamydia trachomatis* serovars L1, L2, L3.

Transmission is primarily sexual but close contact with infectious secretions can result in transmission.

Clinical Features

Incubation period is 3–12 days, sometimes longer.

Primary lesion – Lesion is a papule, pustule or small erosion that is often unnoticed and heals after a few days. Lesions are found on glans penis in men and on labia or vaginal walls in women. Extragenital lesions are very uncommon.

Secondary stage (inguinal) – Inguinal and less often femoral lymphadenopathy. The characteristic groove sign is seen when both inguinal and femoral lymph glands are enlarged (Fig. 13). Buboes may develop, if untreated, these often rupture and healing is protracted. Lymphnodes may form small areas of necrosis, which attract neutrophils or form stellate abscesses. Further inflammation may cause loculated abscesses, fistulas and sinus tracts.

Tertiary stage (anogenital-rectal syndrome) – Healing of the secondary stage by fibrosis results in lymphatic vessel obstruction. This takes a few months or years resulting in a 'saxophone penis' in males and 'esthiomene' in females.

Rectal stricture – With progressive stricture formation there is rectal discharge and bleeding, colicky pain and passage of ribbon stools. Rectal strictures are usually 2–3 cm above anocutaneous margin. Complete bowel obstruction is rare.

Clinical and histological picture of LGV proctocolitis may mimic inflammatory bowel disease.

Neoplastic change – as a sequel of genital elephantiasis and anogenital-rectal syndrome.

Diagnosis – (a) Demonstration of *C. trachomatis* from lesion swab (genital bubo aspirate or rectum). Alternatively *C. trachomatis* can be identified by direct fluorescent microscopy. (b) The compliment fixation (CF) test, in a titre of > 1: 250 strongly suggests the diagnosis. (c) Immunoperoxidase test is a rapid test for detecting *C. trachomatis* specific IgG and IgA antibodies. (d) PCR provides accurate diagnosis in low prevalent areas. (e) Enzyme immunoassay is suitable for antigen detection in ulcer scrapings and bubo aspirates.

Differential diagnosis of LGV – (a) Other causes of genital ulceration or acute lymphadenitis such as plague, tularemia, tuberculosis, Hodgkin's disease and cat-scratch disease. (b) Of rectal stricture – trauma, malignancy, TB, schistosomiasis and actinomycosis.

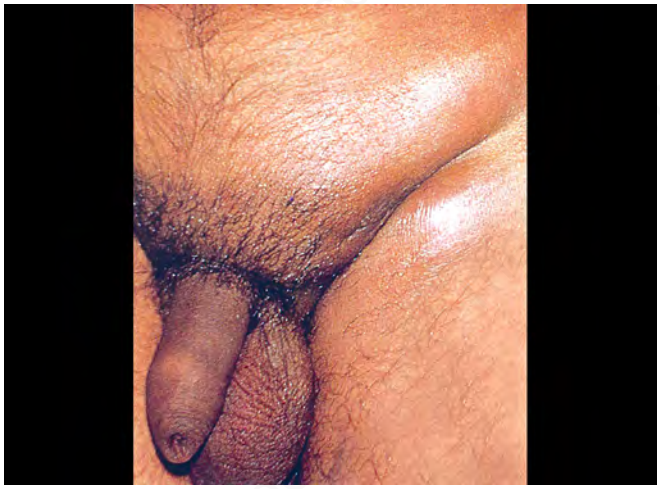


Fig. 13: Lymphogranuloma venereum: typical groove sign due to enlargement of femoral and inguinal lymph nodes

Treatment – (a) Drugs – Doxycycline 100 mg b.d. for 14 days, erythromycin 500 mg q.d.s. for 14 days (in pregnant women), or tetracycline 500 mg q.d.s. for 14 days. (b) Surgical tr. – Hot fomentation for bubo and aseptic aspiration of fluctuant bubo. Rectal strictures require periodical dilatation. Internal proctotomy may be required in some cases. Other indications for surgery are bowel obstruction, and persistent rectovaginal and other fistulae.

2. HIV AND AIDS

HIV: The virus – HIV-1 and HIV-2 are members of the lentivirus family of retroviruses. HIV-1 is probably a cross-species transmission to humans from chimpanzee virus (SIVcpz), whereas HIV-2 probably arose separately from sooty mangabey virus (SIVsm). As a result, HIV-1 and HIV-2 are relatively dissimilar; their nucleic acid sequences are only about 40% homologous. Both viruses are tropic for $CD4^+$ lymphocytes and monocytes and have a similar genetic structure. Both cause AIDS, but HIV-2 appears to be less virulent progressed slowly and is less commonly transmitted vertically.

A CD4 count < 200/μL in and HIV infected individual is defined as AIDS.

Structure of the HIV virion – HIV is an enveloped RNA retrovirus and consists of:

- Outer envelope - Bilipid membrane in which the viral antigens are embedded.
- Inner core bounded by a protein coat containing 3 viral enzymes - Reverse transcriptase, Integrase, Protease.

TRANSMISSION

1. ***Sexual***

   Homosexual – Most HIV infections occur in homosexual and bisexual men who have a large number of sexual partners. The sexual practices often involve anal intercourse and fellatio with ejection of semen into mouth.

   Heterosexual: Multiple heterosexual contacts, often prostitutes.

gp 120 surface envelope	p24 capsid protein
glycoprotein	Accessory proteins
gp41 transmembrane	(Vpr, Vif, cyclophilins)
Envelope glycoprotein	Diploid RNA genome coated
Virus enzymes (e.g. reverse	With p9 nucleocapsid protein
Transciptase, integrase)	Virus envelope derived from
p17 matrix protein	Cell membrane

2. ***Blood and tissue fluids***
   - Contaminated blood and blood products:
     - Blood transfusion.
     - Blood products, e.g. factor VIII.
3. ***Contaminated needles and syringes***
   - Injecting drug use.
   - Needle stick injuries.
   - Inadequately sterilized medical equipment.
4. ***Organ and tissue donations***
   - Semen
   - Kidney, skin, cornea
   - Bone marrow
5. ***Mother to child***
   - In utero
   - At birth
   - Breast milk

Pathogenesis of HIV infection

- HIV virus infects target cells ($CD4^+$ T cells, monocytes, macrophages and dendrite cells) through CD4 receptors.
- On entering T cells, the virus integrates its RNA genome into the host cell genome by first transcribing this genome into DNA (HIV provirus) with the help of enzyme reverse transcriptase.
  - Provirus is then transcribed and translated along with the host cell DNA to synthesize specific viral components, which eventually assemble to produce complete virus particles.
  - At this time patient is seronegative, i.e. antibodies against the virus are not present. But patient is highly infectious. This period is labelled *"window period"*.
  - Although some virions are killed, HIV continues to multiply infecting increasing number of CD4 cells.
  - Clinical manifestations depend on the effect on the immune systems:
- In early stages of immune destruction, the patient is asymptomatic
- As the immunosuppression progresses over a period of time patient becomes symptomatic.

HIV TESTING AND MONITORING

Viral replication occurs during the incubation period, during which the viral genome and briefly, viral p24 antigen may be detected. There is an early 'window' period during which HIV infection cannot be detected, but this can be shortened if samples are tested for presence of HIV genome.

HIV diagnostic tests can be divided into antibody detection, combined antibody and antigen and genome detection.

HIV antibody and/or antigen tests – In general, an HIV-infected individual should have mounted an antibody response within 6 weeks to 3 months post-exposure. The wide range of diagnostic HIV assays include several combined HIV-1 and HIV-2 antibody tests, with or without a core antigen (p24) component based on enzyme immunoassay technology (e.g. ELISA). Sensitivity is usually tested by testing conventional panels of sera from patients who have established infection or by testing sequential samples from patients who are seroconverting.

Other assay formats use HIV-1 viral lysate, HIV-2 synthetic peptides and HIV antibody-p24 antigen combination assays.

HIV type discrimination can be undertaken using an immunoblot format. Specific HIV-1 and HIV-2 proteins are electrophoretically blotted onto a nitrocellulose membrane that binds HIV antibodies in the blood sample.

Diagnosis of HIV infection in blood samples from babies is more difficult because of the presence of passively-acquired maternal antibody. This wanes over 12–16 months, but infection can be demonstrated earlier by examining blood samples for HIV proviral DNA or HIV RNA.

Confirmatory testing – After HIV antibody has been detected in a separated serum sample using one assay, a second test on the original unseparated sample must be performed using a different assay format.

HIV genome detection – Plasma HIV load testing is performed to assess disease progression and response to antiretroviral therapy. Viral replication is a dynamic process, and HIV RNA levels may be low in the early stages of infection. Higher levels are correlated with increased risk of disease progression.

HIV RNA can be quantified using several assays using different methodologies:

1. *Reverse transcription polymerase chain reaction* (RT-PCR) involves reverse transcription of target RNA to generate complimentary DNA (cDNA). PCR amplification of cDNA is followed by hybridization of oligonucleotide probes and detection of cDNA-bound probes by colorimetric analysis.
2. *RNA transcription* – The signal amplification probe method involves a set of oligonucleotide capture probes that bind the viral RNA to microwell. A set of target probes hybridize to both the viral RNA and pre-amplifier probes. The latter bind to the amplifier probe, forming the branched DNA complex.
3. *An enzyme-labelled probe* binds to the immobilized complex and is detected by a chemiluminescent substrate that is broken down by the enzyme. Light emission is directly proportional to the amount of HIV-1 RNA in the sample.

HIV drug resistance – is said to occur when the susceptibility of the virus to one or more specific antiviral drugs is reduced. This is measured in phenotype assays, and resistance expressed as fold reduction in drug susceptibility compared with a wild-type (drug-sensitive) strain.

Genotypic assays – Specific mutations can be identified by nucleic acid sequencing of plasma virus. This technique is called 'genotypic resistance assay'. A number of key mutations have been identified which are associated with reduced drug susceptibility to one or more antiretroviral drugs.

Recombinant virus assays in which reverse transcriptase and the protease gene from the patient's plasma, amplified by PCR, are recombined with a laboratory strain of virus thus generating a recombinant virus containing the reverse transcriptase and protease generated from the clinical sample. This virus can be rapidly screened for drug susceptibility.

Natural history of HIV infection

The clinical spectrum of HIV infection ranges from asymptomatic state to severe illness due to a variety of opportunistic infections. HIV infected individuals are permanently infectious, and hence transmit the virus to others in the asymptomatic stages.

STAGES OF HIV INFECTION

(WHO staging) See Table 3.

Acute retroviral syndrome (ARS) – A manifestation of primary HIV infection occurs 2–3 weeks after infection.

Clinical features

- Symptoms - Fever, headache, vomiting, sore throat, arthralgia, myalgia
- Cutaneous - Maculopapular rash, mucosal ulceration (mouth, oesophagus, genitals)
- Lymphoreticular - Lymphadenopathy, hepatosplenomegaly

Investigations – (a) Haematological - (i) Initial lymphopenia followed by lymphocytosis. (ii) Depletion of CD4 cell with CD8 lymphocytosis. Atypical lymphocytes. (b) Viral markers - (i) HIV RNA detection. (ii) P24 antigen in 1/3 patients. (iii) Serology - Antibody tests negative in early stages. Anti-HIV IgM may be detected.

Tr. Anti-retroviral therapy protects susceptible CD4 cells from HIV infection.

Table 3: Stages of HIV infection

Primary HIV infection
• Asymptomatic
• Acute retroviral syndrome: Fever with maculopapular rash primarily on trunk with small aphthous lesions on oral and genital mucosa
Clinical stage 1
• Asymptomatic
• Persistent generalized lymphadenopathy
Clinical stage 2
• Unexplained moderate wt. loss (< 10% of presumed body wt.)
• Infections
• Recurrent resp. tract infections
• Herpes zoster
• Fungal infections of finger nails
• Oral lesions
– Recurrent oral ulcerations
– Angular cheilitis
• Itchy dermatosis
– Papular pruritic eruptions
– Seborrhoeic dermatitis
Clinical stage 3
Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations.
• Unexplained symptoms
– Chronic diarrhoea for > 1 month
– Persistent fever, intermittent or constant for > 1 month
• Severe wt. loss (> 10% of presumed or measured body weight)
• Infections
– Severe presumed bacterial infections
– Pulmonary tuberculosis diagnosed in last 2 years
• Oral lesions
– Oral candidiasis
– Oral hairy leukoplakia
– Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
• Conditions where confirmatory diagnostic testing is necessary
– Unexplained anemia (< 8 g/l or neutropenia (< 500 µl) or thrombocytopenia (< 50,000 µl) for > 1 month
Clinical stage 4
Conditions where a presumptive diagnosis can be made on the basis of clinical signs and simple investigations
• HIV wasting syndrome
• Infections
– Pneumocystis pneumonia
– Recurrent severe or radiological bacterial pneumonia
– Chronic herpetic simplex infection (oral, labial, genital or anorectal of > 1 month duration).
– Oesophageal candidiasis
– Extrapulmonary tuberculosis
• Neoplasms
– Kaposi's sarcoma
• Neurological disease
– CNS toxoplasmosis
– HIV encephalopathy

Contd...

LABORATORY DIAGNOSIS OF HIV

Tests for HIV specific antibodies in serum/plasma

Screening tests – for screening antibodies against HIV in patient suspected of being HIV infected. They are also used for screening blood and blood products and have a high sensitivity and positivity.

1. ELISA or EIA useful test can be modified frequently, to quantify the result (number of viral copies/mL). Time required 60–90 min.
2. Rapid tests - Useful in emergency clinics, causalities and trauma. Time required < 30 min.

Supplemental tests are used to confirm positive results of screening tests. These tests are false negative in early stage of infection as they are not so sensitive.

Western block (WB) is a specific test for detecting antibodies to different HIV antigens. A modified Western block can differentiate HIV-1 and HIV-2.

Combination of two or more EIAs, using different antigens can provide a more reliable information than ELISA/WB combination, at a lower cost.

Immunoblot (IB) test also allows differentiation between HIV-1 and HIV-2 infections.

Indirect immunofluorescent antibody assay is an expensive test and results are same as Western block.

Confirmatory tests – to confirm presence of virus in the person who is either positive or has equivocal results to HIV-specific antibodies.

Detection of viral RNA by PCR, the first test to become positive.

Detection of HIV-specific core antigen (p24) in the serum during the window period, during late stage of the disease, in HIV-infected new-borns, for monitoring antiretroviral therapy and in cases of HIV associated encephalopathy in CSF.

Virus isolation: HIV can be cultured from blood or any other body fluid of the infected individual.

Table 4: Conditions where confirmatory diagnosis testing is necessary

• Bacterial infections
– Disseminated non-tuberculous mycobacterial infection
– Recurrent nontyphoidal salmonella septicaemia
• Fungal infections
– Extrapulmonary cryptococcosis including meningitis
– Candidiasis of trachea, bronchi or lungs
• Viral infections
– Visceral herpes simplex infection
– Cytomegalovirus infection (retinitis or infection of an organ other than liver, spleen or lymphnodes)
– Progressive multifocal leucoencephalopathy
• Protozoal infections
– Cryptosporidiosis
– Atypical disseminated leishmaniasis
• Neoplasia
– Lymphoma (cerebral or B-cell non-Hodgkin)
– Invasive cervical carcinoma

Tests for diagnosis of disease progression and complications

Viral load estimation – Quantitative HIV RNA estimation is useful for diagnosing acute HIV infection and for predicting probability of transmission, rate of progression in chronically infected patients and for therapeutic monitoring. Treatment failure is defined as failure to decrease viral load by 1.5 log 10 c/mL within 4 weeks or to achieve undetectable virus status by 4 months.

CD4 cell count is a standard test to assess progression to AIDS and make decisions about antiviral therapy, and prophylaxis for opportunistic infections. The normal values range from 800 to 1050 cells/mm^3. The count should be repeated very 2–4 months in patient on ART.

Diagnosis of HIV in newborn is done by one or more combinations of detection of IgA and/or IgM anti-HIV antibodies, estimation of p24 antigen, PCR, or in vitro antibody production assay, in vitro isolation of virus from blood or tissues and indirect indicators of HIV infection.

CLINICAL MANIFESTATIONS OF HIV

Primary HIV infection – may be asymptomatic, subclinical or clinical. Clinical illness is usually self-limiting, and several manifestations can occur, including a 'glandular fever-like' illness, meningoencephalitis and peripheral neuropathy. Seroconversion time (defined as the time from infection to detection of specific antibodies) is 8 days to 10 weeks after onset of acute illness. Rarely, severe immuno- suppression occurs during acute HIV infection, and AIDS illnesses such as oesophageal candidosis and *pneumocystis jiroveci* pneumonia have been reported.

Early manifestations of HIV infection – Individuals may be asymptomatic or have enlarged lymphnodes with or without minor symptoms, e.g. tiredness, lethargy, excessive sweating, and pains in muscles or joints.

Bacterial sepsis manifests as pneumonia, bacteraemia or both.

Later manifestations – In addition to AIDS, other manifestations that indicate a serious prognosis:

- Constitutional symptoms and/or unexplained diarrhoea, fever (> 38°C) for > 1 month or unexplained weight loss of > 10% body weight.
- Neurological problems (e.g. neuropathy, myelopathy).
- Recurrent *Salmonella* bacteraemia, extensive herpes zoster, recurrent oral candidosis and oral hairy leukoplakia.

Opportunistic infections in HIV disease

Opportunistic infections (OIs) occur in HIV disease due to progressive deterioration in immune status as a result of steady decline of CD4 helper lymphocyte number. CD4 cell count remains the best marker of immune status in HIV disease.

Tuberculosis, herpes zoster and Candida albicans tend to develop when CD4 count is < 500/mm^3. *Pneumocystis jiroveci* pneumonia, occurs when CD4 count is < 200/mm^3. Toxoplasmosis, cryptococcosis, cytomegalo- virus infections occur when CD4 count is < 100/mm^3. Mycobacterium avian complex and systemic fungal infections occur when CD4 count is < 50/mm^3.

Pneumocystis jiroveci pneumonia (PJP). *Cl. Fs.* – Dyspnoea, fever, cough. Physical examination is usually normal. Chest X-ray is variable, interstitial pattern is most common. Elevated lactate dehydrogenase and exercise desaturation are highly suggestive. *Tr.* – Trimethoprim -sulphamethoxazole DS 2 tds for 21 days. In severe disease Prednisolone 40 mg bd for 5 days, then 20 mg od for 12 days. Patients who have not had HAART should finish therapy for PCP prior to starting HAART, those on HAART should continue anti-retroviral drugs.

Tuberculosis is the earliest HIV-related OI. It is the commonest of all OIs, is also the commonest cause of death in patients with AIDS. It is also the only transmissible OI. TB accelerates and negatively impacts the course of HIV disease.

Cl. Fs. – With preserved CD4 counts (< 200/mm^3), typical radiological features are upper lobe infiltrates and cavitation are common. As the CD4 count falls, atypical features like focal, nodular and often lower lobe infiltrates occur. Extra-pulmonary TB is more common at low CD4 counts.

Tr. – Standard first line drugs should be used for 6 months, or 9 months if response is slow. DOTS should be used whenever possible with drug level monitoring in non-responders as malabsorption is not uncommon.

Whilst symptoms improve, chest radiographs resolve and sputum converts at the same time period in HIV +ve and -ve patients, these patients still have a high mortality. Much of the excess mortality is from non-tuberculous AIDS-related conditions. This has been referred to as 'treatment paradox'.

Paradoxical reactions are fairly frequent when HAART is started in patients with TB. These are transient worsening or appearance of new symptoms, signs or radiographic manifestations. Clinical manifestations are diverse and treatment involves discontinuation, NSAIDs, or steroids.

Toxoplasma encephalitis presents with neurological symptoms including sensorimotor deficits, seizures, confusion, ataxia and headaches. Toxoplasma IgG antibody is positive. *Tr.* – Pyrimethamine 100 mg loading dose followed by 50–75 mg/day, sulphadiazine 4–8 g/day, followed by lifelong suppressive treatment as relapses are common.

Cryptococcal meningitis. Onset is often indolent with fever, headache, and occasional meningeal signs. *Tr.* – Amphotericin B with or without Flucytosine for 2 weeks followed by lifelong therapy with fluconazole.

Candidiasis – often presents with odynophagia and wt. loss. Oropharyngeal thrush and oesophageal candidiasis respond well to Fluconazole 100–200 mg/day for 2–3 weeks.

Atypical mycobacterial infections (MAC) are rare. It has been suggested that prior infection with *M. tuberculosis* reduces risk of MAC disease. It usually presents with fever, wt. loss, diarrhoea and bone marrow, liver and spleen involvement. *Tr.* – Clarithromycin with ethambutol.

Cardiac complications include pericardial effusion, disturbances of rhythm, malignant infiltration. Heart muscle disease can be of three forms – global left ventricular dysfunction (more common in late HIV disease), isolated right ventricular dilatation and borderline LV dysfunction. Cause of heart muscle disease related to HIV is unknown, but it may be related to the idiopathic lymphocytic myocarditis often found in patients with ventricular dysfunction.

Incidence of pulmonary hypertension is about 0.5%.

Neurological Complications

The central and peripheral nervous systems are involved at every stage of HIV infection.

Meningeal involvement – (a) *TB meningitis* tends to occur in late latent stage with CD4 count < 300 mm^3. (b) Commonest chronic meningitis is due to *Cryptococcus neoformans.* About half present with typical features of meningitis. The other presentations range from isolated headaches to cognitive impairment.

Non-focal brain involvement

AIDS-dementia complex (ADC) or HIV associated dementia is a syndrome of insidious onset cognitive decline and behavioural changes with motor dysfunction. In later stages affected individuals are demented with incontinence, paraparesis, and ataxia.

Encephalopathies in later stage of HIV infection usually due to metabolic complications are unusual and difficult to diagnose.

Focal CNS disease

Cerebral toxoplasmosis due to reactivation of T. gondii infection has already been discussed. CT or MRI show single or multiple inflammatory mass lesions with oedema and ring enhancement, typically located in basal ganglia.

Progressive multifocal leucoencephalopathy caused by JC virus produces multiple focal, demyelinating lesions in subcortical white matter with corresponding deficits which evolve clinically over weeks or months.

Primary CNS cell lymphomas are of B cell origin and produce focal deficits. Diagnosis requires stereotactic brain biopsy.

Mass Lesions in CNS in HIV

Four common differential diagnosis are toxoplasmosis, tuberculoma, PML primary CNS lymphoma.

Spinal cord diseases

Tubercular and pyogenic infections and lymphoma can produce arachnoiditis and spinal cord compression due to vertebral disease. The typical cord pathology of HIV is vacuolar myelopathy. It is usually associated with ADC and the typical sensory neuropathy of HIV.

Cytomegalo virus can produce an unusual rapidly developing cauda equina syndrome in patients with advanced HIV disease. Tr. Ganciclovir, cidofovir and foscarnet to prevent ventriculoencephalitis which can be fatal.

Peripheral neuropathies occur at all stages of the infection. (a) Distal sensory polyneuropathy presents with paraesthesiae to severe neuropathic pain. (b) Inflammatory demyelinating neuropathies resembling G-B syndrome and chronic IDP occur in early to mid-stage HIV infection.

Table 5: Oral manifestations of HIV/AIDS

- Candidiasis: Pseudomembranous, erythematous, angular cheilitis
- Gingivitis/periodontitis
- Necrotizing stomatitis
- Herpes simplex: Intraoral, perioral
- CMV infection
- Herpes zoster
- Aphthous ulcer: Minor, major or herpetiform
- Hairy leukoplakia
- Salivary gland enlargement with xerostomia
- Oral Kaposi's sarcoma: Brown, red or blue or purple macule or nodule particularly on hard palate and attached gingiva
- Oral warts/papilloma
- Focal epithelial hyperplasia

Myopathies – Patients present with weakness and myalgia. Inflammatory myopathies can develop both in early infection as well as with immune reconstitution.

AIDS and the GI Tract

Oral manifestations

See Table 5.

Oesophageal symptoms

Candidosis. Diagnostic criterion for AIDS in HIV positive patients. Pain on swallowing and dysphagia. Good response to fluconazole 400 mg single dose. If resistance itraconazole solution 200 mg/day for 2 weeks.

Ulceration

- *CMV infection* may produce ulcers of lower oesophagus or hemorrhagica oesophagitis. Both respond to i.v. ganciclovir 5 mg/kg b.d., or foscarnet 90 mg/kg b.d. for 2 weeks (in those with normal renal function).
- *HSV infection* less commonly produces discrete oesophagitis with associated fluid-filled vesicles. Tr. – Acyclovir 400-800 mg 5 times daily. Can be given i.v. 5 mg/kg t.d.s.
- *Ulcers of unknown aetiology* – Large shallow ulcers resembling aphthous ulcers. Prednisolone 40 mg/day or intralesional methylprednisolone acetate may be effective.

Wasting. Loss of more than 10% of ideal body wt. without obvious cause. Continuing wt. loss is usually associated with a specific pathogen most commonly a protozoal gut infection. *Tr.* – Testosterone 40 mg t.d.s., anabolic steroids or appetite stimulants. Recombinant growth hormone 0.1 mg/kg/day increases lean body mass in wasted individuals.

Diarrhoea is the presenting feature in up to 30%. Homosexuals acquire a variety of sexually transmitted enteric infections (collectively termed 'gay bowel syndrome').

Bacterial Infections

Salmonella and Campylobacter infections. Septicaemia (20-40%) and a relapsing course (10-20%) are seen particularly in those with low CD4 + lymphocyte counts. *Tr.* – Ciprofloxacin 250–500 mg b.d.

Mycobacterium avium-intracellulare (MAI) causing diarrhoea. Jejunal biopsies (showing MAI-laden macrophages in lamina propria) may be necessary in establishing the cause. *Tr.* – Azithromycin 1 g/day and clarithromycin 1 g/day produce marked improvement in systemic manifestations with variable effects on diarrhoea.

Protozoal Infection

Cryptosporidiosis causes diarrhoea. Cryptosporidium can be identified in stool samples and is occasionally seen on gut biopsy when direct faecal analysis is negative. The infection responds to HAART. No medication has been shown to eradicate cryptosporidia from stool, though paromomycin 500 mg q.d.s. may reduce stool volume by up to 50%.

Microsporidia – Encephalitozoon and the closely related *Septata* have also been associated with diarrhoea. Most patients have marked immuno-suppression, wasting and diarrhoea of up to 1 litre/day. Diagnosis is by staining faecal samples with strong trichrome or a fluorescent stain, which demonstrates the spores. *Tr.* – Albendazole 400 mg b.d. HAART eradicates all types of microsporidia within 6 months of initiation.

CMV infection of the colon causes abdominal pain, rebound tenderness and diarrhoea which may be bloody. Toxic dilatation and perforation are complications. Multiple CMV inclusions with intense inflammation on rectal biopsy confirm the diagnosis. *Tr.* – Ganciclovir or Foscarnet.

Abdominal pain. Infection is the cause in most patients.

(a) *Right upper quadrant* pain is often associated with changes of sclerosing cholangitis or bile duct dilatation. (b) *Right iliac fossa* pain is often caused by appendicitis which may be more common because of CMV infection. (c) *Diffuse abdominal* pain, often associated with rebound tenderness, is usually caused by CMV infection.

Hepatitis

Hepatitis D virus infection occurs in two ways (a) To serum containing both HBV and HDV. It results in mild to fulminant hepatitis.

(b) Superinfection of chronic HBV carrier with a new inoculum of HDV results in – (i) Mild HBV may become fulminant hepatitis. (ii) Acute severe hepatitis. (iii) Chronic progressive disease resulting in cirrhosis.

Hepatitis C virus infection – Co-infection with HIV may accelerate the natural course of the disease resulting in progressive liver disease.

Pancreatic disease. Prevalence of acute pancreatitis can be as high as 45% probably because it is associated with various drugs used in AIDS.

Dermatological

- Superficial fungal infection: Candidiasis, dermatophytosis, pityrosporum infection
- Disseminated fungal and protozoal infection: Cryptococcus neoformans infections, histoplasmosis, sporotrichosis, dermal leishmaniasis, coccidioidomycosis
- Bacterial and mycobacterial infections: Staph. aureus, M. avium intracellulare, M. tuberculosis, actinomycosis.
- Viral: HPV infection, molluscum contagiosum, herpes simplex virus, varicella and herpes zoster, cytomegalovirus, E-B virus.
- HIV-related rash: Acute HIV exanthem, papular rash of HIV
- Pruritic papular and follicular eruptions: Folliculitis – Eosinophilic pustular, pityrosporum, demodectic. Insect bite reaction. Prurigo nodularis.
- Papulosquamous disorders: Seborrhoeic dermatitis, psoriasis, Reiter's syndrome, atopic dermatitis, lichen planus
- Malignancies: Kaposi's sarcoma, squamous cell and basal cell carcinoma, malignant melanoma
- Miscellaneous dermatoses: Acquired ichthyosis, chronic photosensitivity, granuloma annulare, vitiligo, immunobullous disorders, Sjogren's syndrome, porphyria, telangiectases, leukocytoclastic vasculitis, scabies (Norwegian), hidradenitis suppurativa, palmoplantar keratoderma.

HSV infection – Chronic HSV infection of skin or mucous membrane for longer than one month is an indicator for diagnosis of AIDS. In patients with a history of sexually acquired HSV, the infection usually presents as genital or oral ulceration.

Herpes zoster occurs both early and late in HIV disease. In fact HIV disease is multidermatomal (i.e. affected dermatomes are not adjacent or connected).

Bacillary angiomatosis is a chronic bacterial infection most commonly involving the skin. The causative agent is related to either *Rochalimaea quintana* or *Bartonella bacilliformis.* Skin lesions appear similar to granulation tissue or slowly healing sores. Visceral disease without skin disease may occur, involving the liver, spleen or bones. The condition must be considered in patients presenting with hepatosplenomegaly. *Tr.* Erythromycin or doxycycline for 6–8 weeks.

Haematological abnormalities. Severe neutropenia occurs in as many as 70% of patients and is often related to concomitant drug therapy. In addition there is evidence of defective neutrophil function in HIV/AIDS (chemotaxis, bacterial killing, phagocytosis and superoxide production).

HIV-related thrombocytopenia. An ITP-like syndrome occurs before the onset of AIDS, but is a relatively benign condition. Major life-threatening hemorrhage is rare.

Renal abnormalities. A specific HIV-associated nephropathy (HIVAN) presents as severe nephrotic syndrome as a consequence of glomerulosclerosis which may progress to end-stage kidney failure.

Rheumatological Syndromes

See Table 6.

Problems in HIV infected women. Risk of lower genital tract infection is more common. These include vaginal yeast infections, genital herpes, *Trichomonas,* and pelvic inflammatory disease. Cervical intraepithelial neoplasia can occur, but cervical cancer is seldom listed as a cause of HIV-related death.

Table 6: Rheumatological manifeastations in HIV infection

Due to impaired immunosurveillance • Infectious arthritis • Osteomyelitis
Due to host response to HIV • Polymyositis • Vasculitides • Diffuse infiltrative lymphadenopathy syndrome (DILS)
CD4 defects and persistence of antigens • Reiter's syndrome • Psoriatic arthropathy • Undifferentiated spondarthropathy
Due to chronic immune stimulation • Arthralgias • Painful articular syndromes

HIV-related cancer

Kaposi's sarcoma

Epidemiology – Kaposi's sarcoma is the most common malignancy associated with HIV-1 infection. It seldom occurs in absence of HIV infection, but there are three other epidemiological forms in which the disease is less aggressive – 'classic' (found in elderly Jews and Eastern European men), endemic (initially found in sub-Sahara Africa) and transplant-associated.

Aetiology and pathology – Kaposi's sarcoma-associated herpes virus (human herpes virus 8) is a DNA virus thought to be an essential, though not necessarily sufficient factor in the causation. It has been found in affected tissue. Microscopically it comprises groups of spindle-shaped cells separated by slit-like vascular spaces containing RBCs and mingled with endothelial-lined vessels.

Clinical features and diagnosis – Kaposi's sarcoma can affect any site other than the CNS. Its course is increasingly aggressive and is potentially fatal.

Description – Lesions occur in a multifocal manner. Most patients present with mucocutaneous disease, commonly affecting the limbs, face, trunk and hard palate. Lesions start as areas of red or purple discolouration, then progress to firm, raised, non-tender nodules or plaques, which turn brown over time. In dark-skinned individuals, the lesions are brown or black.

Lymphoedema occurs as a result of small lymphatic obstruction, and affects mainly the lower limbs, can be severe in nature and lead to cellulitis. Associated lymphadenopathy should be biopsied to exclude concurrent lymphomatous disease.

Most common visceral sites are: (a) GI tract – Kaposi's sarcoma can occur throughout the GI tract and is diagnosed on endoscopy. (b) Pulmonary Kaposi's sarcoma may present with cough, wheeze, shortness of breath on exertion and haemoptysis. Reticular nodular shadowing, pleural effusions and lymphadenopathy are seen on chest radiography, but the appearances are nonspecific and may resemble *Pneumocystis jiroveci* pneumonia. Visualization of characteristic lesions on bronchoscopy is required to make a diagnosis.

Management – There is no cure for AIDS-related Kaposi's sarcoma. HAART may lead to regression. Radiotherapy is used for symptom control and for patients who are too ill to receive systemic treatment. Alternatives include cosmetics, cryotherapy, intralesional injections of vinblastine or interferon and topical retinoids.

Low CD4 count, prior opportunistic infection, visceral disease, and B symptoms (sustained fever > 38°C, night sweats, weight loss > 10% body wt.) are poor prognostic factors.

Systemic non-Hodgkin's lymphoma (NHL) develops in 10–20% of HIV-positive individuals, and may occur late in HIV disease. AIDS-related lymphomas are usually high-grade. Most patients present with advanced-stage and extranodal disease (meninges and bone marrow).

Primary cerebral lymphoma represents 15% of AIDS-related lymphomas. Presentation is with neurological deficit with multiple enhancing lesions on CT or MRI. Diagnosis can be confirmed by open or stereotactic biopsy.

Cervical carcinoma. Both HPV infection and cervical intraepithelial neoplasms (CIN) are more common in women with HIV infection.

Paediatric HIV Infection

Mode of acquisition. 90% of HIV infection in children is MTCT.

Incubation period and disease progression. HIV infection if acquired in early life has a much shorter incubation period due to immunological immaturity. 10-30% are rapid progressors and can die within 5 years.

Cl. Fs. Infected children present with non-specific common childhood disease. Diarrhoea and respiratory infections are common, recurrent, persistent, and more severe. Others include recurrent fever, failure to thrive, hepatosplenomegaly, oral thrush, lymphadenopathy, anemia, TB and bronchiectasis. Pneumocystis pneumonia can occur in first year of life even with normal CD4 counts. Developmental delay and interstitial pneumonia are unique features.

Classification of disease severity

Category N: Asymptomatic children, without signs or symptoms, or who have only one of the conditions listed in category A.

Category A: Two or more symptomatic HIV-related conditions such as lymphadenopathy, hepatomegaly, splenomegaly, dermatitis, parotitis, recurrent upper respiratory infections, otitis media and no documented B or C clinical conditions.

Category B: Defines children with moderately symptomatic, HIV-related conditions – single episode of bacterial meningitis, pneumonia or sepsis, fever lasting for more than one month, recurrent or chronic diarrhoea, anemia, neutropenia or thrombocytopenia persisting more than 30 days, cardiomyopathy, nephropathy, hepatitis, lymphoid interstitial pneumonia (LIPO), CMV infection before 1 month of age, persistent oral, disseminated varicella-zoster viral infections, herpes zoster (2 dermatomes/2 epi-

sodes), and recurrent Herpes simplex stomatitis without any category C conditions.

Category C: These are AIDs defining conditions and include recurrent, severe infections (meningitis, pneumonia, septicaemia, etc.), oesophageal/pulmonary candidiasis, cryptosporidiosis, CMV/toxoplasmosis disease of more than 1 month of age, recurrent nontyphoidal salmonella septicaemia, disseminated/extrapulmonary mycobacterial tuberculosis, atypical mycobacterial infections, wasting syndrome, pneumocystis jiroveci pneumonia, and HIV encephalopathy.

The severity of illness can also be assessed by the CD4 cell count. The CDC classification and immunological classification can be combined together.

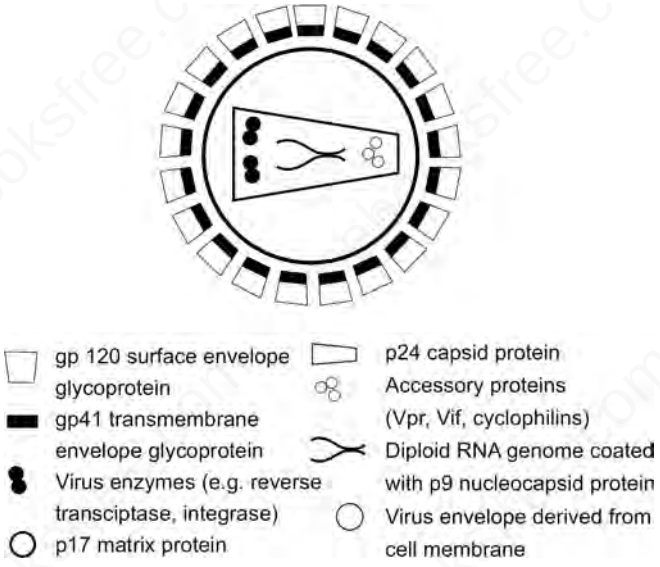
Antiretroviral therapy

Definite indications

- Age < 12 months – Any clinical symptom of HIV (category A, B and C) or immune suppression (immune category 2 or 3)
- Age > 12 months – Category C disease or immune category 3 in children above 10 months, a positive ELISA, and a confirmatory test in form of DNA/RNA PCR or western blot in children below 18 months, presence of transplacentally transmitted material antibodies makes standard HIV IgG antibody tests unreliable. Alternative tests include HIV 'c' culture, HIV PCR or p24 antigen testing.

Prevention of mother to child transmission of HIV

MTCT of HIV-1 can occur during pregnancy, labour or breast feeding.



Therapy – Short course regimens (usually comprising ZDV, 3TC, NVP) are well tolerated with no reported teratogenicity. However with short course partly suppressive drug regimes is the risk of drug resistance and limitation of future treatment options.

If HAART is not indicated, the PHPT-2 regime is preferred. Other options are – (a) AZT-3TC (from 36 weeks intrapartum and 1 week postpartum and 1 week to neonate). (b) Antenatal (28 weeks onwards) intrapartum and neonatal 1 week AZT.

If mother has not received any therapy the infant may be given single dose NVP with 1 week AZT, starting as soon as possible after and definitely within 48 hours.

Elective Caesarean section reduces MRCT by 55–85% as compared to vaginal delivery irrespective of AZT therapy. Risk of postoperative complications is slightly higher than with vaginal delivery. The risk further increases with emergency CS and with advanced HIV disease.

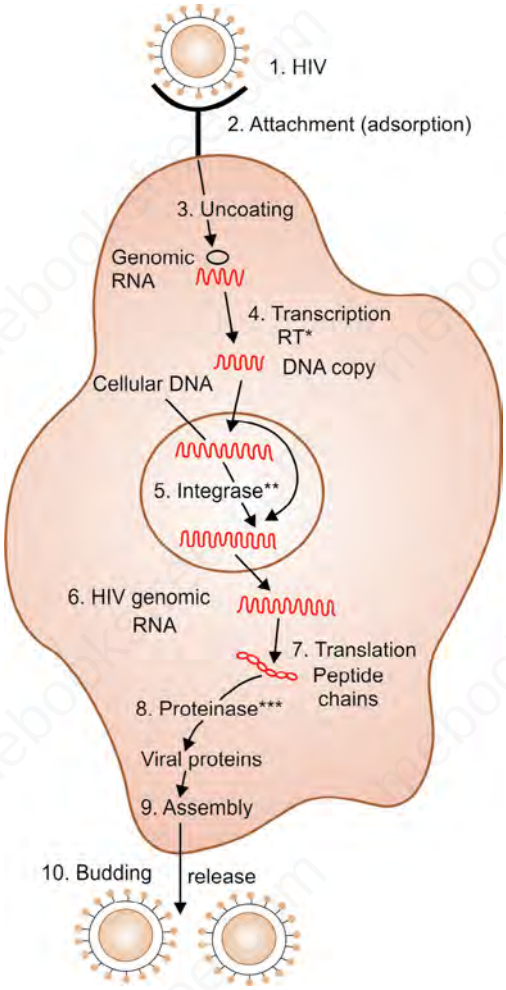


Fig. 14: Sites of Action for Several important Classes of Inhibitors *NRTIs, NNRTIs act here; ** Integrase inhibitors act here; ***PIs act here

Infant feeding. Breast feeding increases transmission rate and greatly reduces efficiency of prophylactic ARV regimes.

The risk is greatest in first 6 months but persists as long as breast feeding continues. Mixed feeding may be more risky than exclusive breast-feeding as allergic reactions to replacement feeds may damage intestinal mucosa and facilitate entry of the virus. If it is decided to have exclusive breast feeding it should be with early and rapid weaning at 4–6 months. Other options such as wet nursing by HIV-negative relative or heat treatment of expressed breast milk are not very practical but may be considered.

Antiretroviral therapy

Drugs

Major classes of antiretroviral drugs

1. Nucleoside analogue transcriptase inhibitors (NRTIs)
2. Non-nucleotide reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)

Initial evaluation – Before starting ART the following investigations are necessary:

- History of or presence of any STDs, VDRL/TPHA, if necessary.
- Chest radiograph or CT scan to exclude TB or any other infection.
- LFTs and tests to rule out coinfection with hepatitis B or C.
- History of alcohol intake or drug abuse.
- History of previous ART therapy by patient or partner.
- CBC – Zidovudine is contraindicated, if anemia.
- Testing for HIV-1 and HIV-2. Use of NNRTIs is not effective against HIV-2 virus.
- CD4 counts should be done at the same time each day because of diurnal variations. CD4 counts may be low with opportunistic infections like tuberculosis.
- CD4 counts should be done as soon as blood is taken or at least within 24 hours.
- A high plasma viral load (PVL) leads to a sharper fall in due course. The main value of PVL assays is in estimating the effectiveness of the antiviral therapy being used resulting in complete viral suppression (≤ 50 copies/mL or < 500 copies/mL) depending on the assay used.

TIME OF INITIATION OF ART

- All patients with CD4 count < 200 require ART.
- All patients with CD4 count < 350, ART can be deferred.
- Patients with high viral loads CD4 count between 200 to 350, starting ART depends on patient's plasma viral load. If > 50,000 copies/mL there is faster progression to AIDS and a sharper rate or decline in CD4 counts.
- In patients with opportunistic infections, ART must be combined with therapy for various OIs. However it is preferable to defer ART until treatment of OI medication has been completed or at least until the patient has been stabilised on the OI medication used, because of poor patient tolerance and toxicity and subject to interactions. Also delaying ART with patient on OI reduces the incidence of immune reconstitution inflammatory syndrome (IRIS), avoiding large tablet burdens and allowing to identify the responsible drug when multiple toxicities could occur.

Plasma HIV RNA level is the stronger predictor of progression rate, except in patients having low CD4+T cell counts. Therapy is generally recommended in patients with plasma HIV RNA levels > 30,000 copies/ml, irrespective of CD4+T cell count, and for patients with CD4+T cell counts < 350/cmm (350/mL) irrespective of RNA level.

Resistance. Development of resistance is a problem, common to all drugs used to treat HIV disease and is characterized by mutations at specific codons on either the reverse transcriptase gene or the protease gene in HIV. Use of drugs with different sites of action delays onset of resistance.

An important technique is the assessment of lymphocyte function and response to antigens as a means of evaluating the function of the immune system, benefits of therapy and need for prophylactic medication.

ANTIRETROVIRAL DRUGS

NRTI-based regimens

Preferred regimens

- Efavirenz + Lamivudine + Zidovudine or Stavudine (not in women with chance of pregnancy)

Alternate regimen

- Efavirenz + Lamivudine + Didanosine
- Nevirapine + Lamivudine + Zidovudine, Stavudine or Didanosine

PI-base regimen

Preferred regimens

- Lopinavir + Ritonavir + Lamivudine or Stavudine

Alternate regimen

- Indinavir +Lamivudine + Zidovudine or Stavudine
- Indinavir + Ritonavir + Lamivudine or Zidovudine or Stavudine

Note: Use of highly active anti-retroviral therapy (HAART) involves use of two NRTIS together with one NNRTI or PI.

Immune reconstitution inflammatory response (IRIS) is basically a pathological inflammatory response where paradoxical worsening occurs after HARRT, in either previously treated infections or subclinical infection with recovery of immune response. It has been described

with mycobacteria, Cryptococcus neoformans, herpes virus pneumocystis, jiroveci pneumonia. IRIS may occur shortly after the treatment of an opportunistic infection, or a "new" clinical syndrome resulting from a previously unrecognised occult infection.

In pregnancy – ART should be started in an untreated patient on AZT, lamivudine and Saquinavir at the beginning of the third trimester. Nevirapine has also been found to be effective as it passes through the placenta very efficiently. It is given as a single dose to the mother at the onset of labour, and one dose administered to the baby at 48-72 hours. If started early in pregnancy, it is given as an od dosage for 2 weeks and two doses daily thereafter, to be continued till birth.

Table 7: Spectrum of HIV disease

HIV associated disease	*Average duration*	*CD4 cell count*
Acute primary infection	1–2 weeks	1000–500
Asymptomatic	10 years	750–500
Early symptomatic	0–5 years	500–250
Late symptomatic	0–3 years	200–50
Advanced disease	1–2 years	50–0

Prophylaxis – HIV postexposure prophylaxis (PEP) should be started within an hour or two. Depending on the type and seriousness of the exposure, either a basic regimen (AZT + Lamivudine) or an expanded drug regimen (basic regimen + indinavir/nelfinavir) for 4 weeks is recommended.

Addendum

Table 8: Factors that increase risk of MTCT

Primary HIV infection during pregnancy
Advanced HIV disease in mother (low CD4 count, high plasma viral load)
Multiple sexual partners
IV drug abuse
Coexistent sexually transmitted STDs
Low maternal vitamin A levels
Premature delivery
Prolonged rupture of membranes
Chorioamnionitis
Vaginal delivery
Use of invasive techniques during labour
Breast feeding

Table 9: Antiretroviral drugs

Generic name	*Mode of action*	*Dose (for adults > 60 kg)*	*Comments/side effects*
NRTIs: Zidovudine (d4t) Lamivudine (3TC)	Complete with cellular nucleoside for incorporation into HIV DNA strands	200 mg tds 150 mg bd	Nausea, headache, neuropathy, myopathy Active against HBV; rash peripheral neuropathy, acute pancreatitis in children
Stavudine (d4T) Didanosine (ddI)		40 mg bd 125 mg bd	Peripheral neuropathy, hepatitis, pancreatitis Take on empty stomach, alcohol may exacerbate toxicity; painful peripheral neuropathy
Zalcitabine (ddC)		0.75 mg tds	Don't take simultaneously with antacids; peripheral neuropathy
Abacavir		300 mg bd	Up to 3% hypersensitivity reactions resolves within 2 days of discontinuation; don't rechallenge
NNRTIs			
Nevirapine Efavirenz Delavirdine	Bind to reverse Transcriptase	200 mg bd then 200 mg bd 600 mg od 400 mg tds	Rash Initial dizziness, avoid dirithromycin Rash
PIs			
Saquinavir (soft gel caps) Ritonavir	Inhibit protease producing immature defective virus particles	1200 mg tds 600 mg bd	Distress, headache; take with fat containing food; store in refrigerator Take with meals To be refrigerated
Indinavir		800 mg tds	Kidney stones, take on as empty stomach, drink at least 15 l of fluids daily
Nelfinavir		750 mg tds	Diarrhoea Not recommended < 3 years of age

Table 10: Post HIV exposure prophylaxis (PEP)

Recommended HIV PEP. Percutaneous injuries / mucous membrane exposures and non-intact skin.	
Exposure type	
HIV positive class I	
Small volume	Consider basic 2-drug PEP
Large volume	Expanded 3-drug PEP
HIV-positive class II	
Small volume	Recommend basic 2 drug PEP
Large volume	Expanded 3-drug PEP
Source HIV status unknown	
Less severe (secretions)	Generally no PEP warranted; however consider 2 drug PEP for source with HIV risk factors
More severe	Generally, no PEP warranted;
Unknown source	
Less severe (secretions)	Generally, no PEP warranted; However consider 2 drug PEP in settings where exposure to HIV-infected person is likely

Table 11: Presenting symptoms of STDs in men

Symptom	*Causes*
Urethral discharge and/or dysuria	Gonococcus Chlamydia Mycoplasma/Ureaplasma Nonspecific urethritis
Warts Genital ulceration	Human papilloma virus Herpes simplex virus Syphilis Nonspecific pre-malignant dermatoses
Vague genital ache Cold, numb penis Pubic crabs Intrascrotal lumps	Chronic prostatitis Psychosomatic Phthirus pubis Orchitis Epididymal cysts Hydrocele Testicular cancer Torsion of testis
Ejaculatory disorders Haemospermia Balanitis	Often psychosomatic Often no obvious cause Thrush in diabetics Often nonspecific genital dermatoses Poor subpreputial hygiene

Table 12: Genital ulcers

Disease	*Morphology*
Aphthae	Sharply marginated, tender ulcers with ragged base. Recurrent. May be associated with Behcet's syndrome
Chancroid	Painful, multiple nonindurated undermined ulcers with slough on floor of ulcer
Donovanosis	Nontender ulcer with raised border.
	Floor of ulcer shows dark red granulation tissue. Lesion not undermined
Chancre of primary syphilis	Usually single, sharp, punched out ulcer with indurated base. Pale granulation tissue on floor of ulcer
Herpes genitalis	Multiple grouped vesicles with erosions going on to ulceration
Scabies	Superficial ulcers with associated erosions, papules, vesicles and pustules.
Traumatic	Superficial or deep erosion with a clean floor. History of trauma.
Ecthyma	Multiple, rounded ulcers with thick, purulent crusts
Tuberculosis	Tender, indurated papules with ulceration
Tumour	Tumour nodule with induration and ulceration
Wart	Heaped-up cauliflower-like growth with ulceration

CHAPTER

17

Miscellaneous

1. PROLONGED PYREXIA

PYREXIA OF UNKNOWN ORIGIN

The term Pyrexia of Unknown Orgin (PUO) may be used to describe the condition of a patient who has

- An oral temperature of 38°C on at least two occasions
- More for longer than 3 weeks
- No known immunocompromised state
- Diagnosis that remains uncertain after a thorough history-taking, physical examination and the following obligatory investigations: determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures (n = 3); urine culture; chest X-ray; abdominal ultrasonography; and tuberculin skin test (TST).

TYPES OF PUO

- *Classical PUO* – PUO in a non-compromised individual.
- *Nosocomial PUO* – refers to infection arising in hospital (e.g. nosocomial pneumonia in patient on ventilation in ICU). Three days of investigation, including at least 2 days' incubation of cultures, is the minimum requirement for this diagnosis.
- *Neutropenic PUO* – refers to infections, usually endogenous and bacterial, in patient with less than 500 WBC/mm^3.
- *HIV associated PUO* – When temp. > 38°C (101°F) on several occasions over a period of more than 4 weeks in outpatients or >3 days for hospitalized patients with HIV infection. The diagnosis is considered if appropriate investigations over 3 days including 2 days of incubation of cultures reveal no source.

CAUSES

A. ***Infections***
   - *Specific infections*:
     a. Bacterial – Tuberculosis, typhoid, paratyphoid, meningococcemia, brucellosis, septicaemias and pyemias, infective endocarditis, tularemia, listeriosis.
     b. Spirochaetal – Secondary syphilis, leptospirosis, rat bite fever, Lyme disease.
     c. Protozoal – Amoebiasis, malaria, kala-azar, toxoplasmosis, schistosomiasis, trypanosomiasis, trichinosis, *pneumocystis jiroveci* pneumonia.
     d. Viral, rickettsial and chlamydial infections – Epstein-Barr virus, influenza virus, A and B hepatitis, cytomegalovirus, coxsackie virus diseases (group B), HIV infection, psittacosis, Q fever, mucocutaneous lymph node syndrome in children.
     e. Fungal – Actinomycosis, histoplasmosis.

2. *Local septic infections or localised pus* – Sinusitis, mastoiditis, dental abscess, osteomyelitis, mammary abscess, parotid abscess. Lung abscess, bronchiectasis, upper abdominal – hepatic, pancreatic, subphrenic or splenic abscess, cholecystitis, appendicitis. Intrarenal or perinephric abscess. Pelvic abscess.
3. *Local infections without pus formation* – Cystitis, phlebitis, inflamed piles, ulcerative colitis, Crohn's disease, diverticulitis, appendicitis.

B. ***Non-infectious causes***
   1. *Neoplasms* – Hodgkin's disease and other lymphomas, hypernephroma, hepatoma, atrial myxoma, metastasis.
   2. *Blood diseases*–Leukaemia, aplastic anemia, hemolytic episodes.
   3. *Connective tissue diseases* – Rheumatic fever, rheumatoid arthritis, adult Still's disease, polymyalgia rheumatica, polymyositis, polyarteritis nodosa, erythema nodosum, systemic lupus erythematosus.

4. *Vascular disease* – Temporal or cranial arteritis, cerebrovascular accident, myocardial infarction, pulmonary thromboembolism, intravascular catheter, infections.
5. *Trauma* – Crush injury, head injury.
6. *Metabolic* – Gout, porphyria.
7. *Endocrine* – Thyrotoxicosis, Addison's disease, pheochromocytoma.
8. *Hypersensitivity reactions* – Serum sickness, drug fever, e.g. sulphonamides, atropine, morphine, salicylates, phenytoin, methyldopa, isoniazid, iodine. Post-myocardial infarction syndrome.
9. *Heat disorders* – Heat fever, heat hyperpyrexia.
10. *Skin disease* – Pemphigus, bullous dermatosis.
11. *Miscellaneous causes* – Dehydration, Recurrent pulmonary embolism, Sarcoidosis, Thyroiditis, Hemolytic states, Dissecting aneurysm, Whipple's disease, Weber-Christian disease.
12. *Metabolic and inherited disorders* – Familial Mediterranean fever, Fabry's disease (angiokeratoma corporis diffusum), Kawasaki's disease (mucocutaneous lymph node syndrome), hypertriglyceridemia and hypercholesterolemia with pancreatitis, cyclic neutropenia. Hereditary urticaria, deafness, amyloid syndrome.
13. *Thermoregulatory disorders* – Brain tumour, cerebrovascular accident, encephalitis.
14. *Factitious fever* – of the Munchausen type (malingerers).
15. *Inherited disorders* – are uncommon causes, e.g. familial Mediterranean fever. Fabry's disease, hypertriglyceridemia (with abdominal pain, recurrent fever and pancreatitis), primary amyloidosis and CNS conditions with a hypothalamic component (thermoregulatory dysfunction).
16. *Habitual hyperthermia.*

INVESTIGATION OF A CASE OF PROLONGED PYREXIA

History

A. General – Exposure to infection, contact with animals, travel, occupational hazards. Prior abdominal surgery should suggest possibility of subphrenic, pelvic or paracolic abscess. Endocarditis and abscesses are common in intravenous drug users. History of trauma.

B. Symptoms

1. *Onset* – Sudden in pyelitis, pneumonia, influenza. Gradual in typhoid, infective endocarditis, pulmonary tuberculosis, brucellosis, etc.
2. *Rigors* – Malaria (continuous type of fever likely in malignant infection), filaria, empyema, UTI, cholangitis, hepatic or appendicular abscess, septicaemia. Rarely typhoid at onset.
3. *Headache* – Meningitis, typhoid at onset, typhus, encephalitis.
4. *Bodyache* – Influenza, dengue fever, fever of secondary syphilis, brucellosis, rat bite fever, relapsing fever.
5. *Sweating* – Malaria, pulmonary or miliary tuberculosis, influenza, rheumatic fever, amoebic liver abscess, lymphomas, brucellosis, relapsing fever, psychogenic.
6. *Convulsions* – Cerebral malaria, encephalitis, meningitis, apical pneumonia.
7. *Delirium* – Typhoid, typhus, pneumonia, meningitis, septicaemia, plague.
8. *Loss of weight* – Tuberculosis, chronic suppurative disease like empyema or lung abscess; lymphomas, thyrotoxicosis, polyarteritis.
9. *Diarrhoea* – Malignant malaria, typhoid and paratyphoid, thyrotoxicosis, Crohn's disease, ulcerative colitis, tuberculous enterocolitis or chronic dysentery.
10. *Vomiting* – Malaria, meningitis, appendicitis, pyelonephritis.
11. *Sore throat* – Diphtheria, secondary syphilis, agranulocytosis, leukaemia, infectious mononucleosis.
12. *Frequency of micturition* – UTI, tuberculosis of kidney, chronic retrocaecal appendicitis.

Past history – Of rheumatic fever or valvular disease, tuberculous lymphadenitis, pleural effusion, rat bite or parrot bite, syphilis, filariasis.

Personal history (a) Residence in endemic area in kala-azar, amoebiasis, Mediterranean fever, and trypanosomiasis. (b) Occupational history in leptospirosis; history of infection in other members of the family. (c) Contact with domestic or wild animals or birds, such infections can be brucellosis (cattle), psittacosis (birds), leptospirosis (rats, dogs and pigs), salmonellosis (ducks, rats, tortoises, etc), Q fever (cattle and sheep), rat bite fever (rats, ferrets), cat-scratch fever (cats). (d) Contact with persons with tuberculosis. (e) Prior surgery or trauma. (f) Drugs (e.g. carbamazepine, intermittent rifampicin consumption, hydralazine ingestion, monoamine oxidase inhibitors particularly in combination with tricyclic antidepressants).

Physical examination

General Examination

1. *Temperature* – Type of fever – (a) Intermittent – High peaks of fever with subsidence to normal or subnormal levels – Malaria, acute pyelonephritis, filariasis, septicaemia, local and general pyogenic infections. (b) Continuous – Temperature high throughout the day with a difference between maximum and minimum daily temperature of less than 2°F – Typhoid, miliary tuberculosis, infective endocarditis, virus pneumonia, hepatic amoebiasis. (c) Periodic or undulating – Rat bite and relapsing fevers, brucellosis, Hodgkin's disease, relapses of typhoid. (d) Double rise with morning and evening peaks – Kala-azar, malaria, liver abscess, typhoid fever, pulmonary tuberculosis, infective endocarditis, E. coli infections of urinary tract. However, many different temperature patterns may be produced by any one disease. (e) 'Hectic' fever with high peaks and relative bradycardia – adult Still's disease.
2. *Pulse rate* – Relative bradycardia in typhoid, meningitis, influenza, dengue, Weil's disease, adult Still's disease.
3. *Respiration* – Hurried in pneumonia and bronchopneumonia, pulmonary TB, pleural effusion or empyema, miliary tuberculosis, pulmonary infarction.
4. *Anemia* – Malaria, kala-azar, septicaemia, subacute infective endocarditis, chronic sepsis, amoebic liver abscess.
5. *Lymphadenopathy* – (i) *Generalized* – in tuberculous glandular enlargement, secondary syphilis, Hodgkin's disease, infectious mononucleosis, septicaemia, lymphatic leukaemia, histoplasmosis, trypanosomiasis, cytomegalovirus infection, HIV infection. (ii) *Localized in* – infectious mononucleosis, plague, rat bite fever, tick typhus, lymphogranuloma inguinale, tularemia.
6. *Jaundice* – with fever in viral hepatitis, Weil's disease, malaria, infectious mononucleosis, liver abscess.
7. *Toxaemia* – Little or no toxaemia in presence of moderately high fever points to E. coli infection of urinary tract, kala-azar, pulmonary or glandular tuberculosis, localised suppurative process, leukaemia.
8. *Skin* – (a) Rash – in typhoid, typhus, meningococcal meningitis, rat bite fever, trypanosomiasis. (b) Any deposits. (c) Petechial haemorrhages – Cerebrospinal meningitis, septicaemia, Weil's disease, malignant diphtheria, typhus, typhoid, SIE.
9. *Clubbing of fingers* – Bronchiectasis, lung abscess, chronic empyema, subacute infective endocarditis, liver abscess.
10. *Arthritis* – Rheumatic fever, subacute infective endocarditis, brucellosis, gout, meningococcemia, leukaemia, disseminated lupus, polyarteritis nodosa, Lyme disease.
11. *Nails* – Transverse white bands on the nails may be seen in brucellosis.
12. *Herpes labialis* – occurs with pneumococcal infection, streptococcal infection, meningococcemia, malaria, Rickettsial infection.
13. *Nodules* – in rheumatic fever, rheumatoid arthritis, leprosy, erythema nodosum, cysticercosis, polyarteritis nodosa.
14. *Local lesion* – Eschar in mite typhus, flare up of site of wound in rat bite, necrotic papule in tularemia, red macule or papule in Lyme disease.

Systemic Examination

1. *Ears, nose, mouth and sinuses* – for focal sepsis in teeth, tonsils and nasopharynx.
2. *Abdomen*
   - Splenomegaly – Malaria, kala-azar, Hodgkin's disease, infectious mononucleosis, typhoid, septicaemia, miliary tuberculosis, infective endocarditis, histoplasmosis, trypanosomiasis.
   - Hepatomegaly – Hepatic abscess, cholecystitis, malaria, leukaemia, kala-azar, yellow fever, Weil's disease, metastatic cancer.
   - Ascites – TB peritonitis; lymphoma.
   - Localising signs – of appendicular abscess, cholecystitis, colitis, diverticulitis, perinephric abscess.
   - Peritoneal and pelvic – Subphrenic abscess, peritonitis, salpingitis, prostatitis.
   - Testicle – Tuberculosis, teratoma.
3. *Heart* – Pericarditis, endocarditis. Hypertension in chronic pyelonephritis and polyarteritis.
4. *Lungs* – Pneumonia, pleural effusion, pulmonary tuberculosis, empyema, bronchiectasis, lung abscess, actinomycosis.
5. *Head and Neck* – Sinusitis, otitis and mastoiditis, diphtheria, tonsillitis, meningitis, brain abscess, and signs of encephalitis.
6. *Limbs* – Thrombophlebitis, osteomyelitis, cellulitis, filarial elephantiasis. Polyneuritis in polyarteritis.
7. *Rectum* – for missed appendicular abscess.
8. *External genitalia* – for sepsis or neoplasia.
9. *Ocular fundi* – for choroidal tubercles, retinitis, etc.
10. Pacemaker implantation.

INVESTIGATIONS

Initial Investigations

- Chest radiography
- Urinalysis and urine microscopy
- C-reactive protein and ESR
- Blood culture taken at times of fever
- Urea, creatinine, electrolytes, liver function tests.

See Table 1 for futher investigations.

Imaging in PUO

- CT and MRI allow identification of small abnormalities, but depend on anatomical changes that develop over time or may not develop in usual manner in immunocompromised (e.g. neutropenic patients).
- Scintigraphy (e.g. radiolabelled WBC scanning) can detect changes caused by infection or inflammation.
- Scans are chosen to help establish presence or absence of a particular diagnosis, e.g. isotope bone scan in suspected bone or joint infection, and ventilation perfusion scan in those with suspected multiple pulmonary emboli.
- Radiolabelled ciprofloxacin derivatives have been used in attempts to distinguish infection from sterile inflammation.

Invasive Investigations

When diagnosis cannot be made with non-invasive techniques, it is often necessary to obtain tissue for culture and histology. (a) Bone marrow examination and liver biopsy are commonly undertaken as part of the 'blind' investigation of PUO. (b) Other invasive techniques, e.g. bronchoscopy, lung, lymph node or renal biopsy are undertaken if clinically indicated. In addition to culture, the biopsy may be analysed using techniques such as *in situ* hybridization, to identify mycobacterial or viral nucleic acid within the tissue. (c) The role of diagnostic laparotomy has now decreased considerably, though it may be useful in patients with abdominal pain and fever in whom diagnosis remains elusive.

Management – In most patients the cause of PUO is identified within one week of intensive assessment. In the remainder it must be decided whether a therapeutic trial is merited. If the patient is clearly unwell and there is no diagnosis, a trial of antituberculous therapy or corticosteroids can be considered. A diagnosis of tuberculosis becomes likely if there is a response within one week of starting anti-TB therapy. In patients with giant cell arteritis or Still's disease the response to corticosteroids is dramatic.

Table 1: Further investigations

Indication	*Investigation*
Residence in or travel to endemic areas	Repeated blood films for malarial parasites
New/changing heart murmur	Echocardiography (trans-oesophageal) may be needed to reveal small aortic valve vegetations Blood films for Borrelia (relapsing fever) and trypanosomiasis, rickettsia, Coxiella, dengue, filarial and amoebic serology, Schistosoma
Headaches, jaw claudication	Temporal artery biopsy
Microscopic hematuria, kidney impairment	Antineutrophil cytoplasmic antibodies (vasculitis), renal ultrasonography (renal cell carcinoma)
Risk of tuberculosis (contact history, previous tuberculosis)	Culture of sputum, early morning urine, bone marrow and liver biopsies
Injecting drug misuse, 'high-risk' sexual contacts	HIV antibody, hepatitis B and C serology

2. VERTIGO

True vertigo is characterized by a sensation of turning either of the patient or his environment, and is caused by disease of the labyrinth or its central connections.

VERTIGO/DIZZINESS

Classification

Classification as central and peripheral vertigo is not particularly useful since in many cases both central and peripheral systems play a role. Classification based on the pattern with which dizziness occurs.

1. Sudden, serious short lasting.
2. Brief dizziness spells.
3. Chronic, not very severe. Persistent/protracted.
4. Sudden severe gradually diminishing.

Examination

1. General examination, BP, pulse, urine, blood tests.
2. ENT examination: For external auditory canal, ear drums, nasopharyngeal cavity, symmetrical functioning of cranial nerves.
3. Hearing test: Whispering speech. The ring of telephone is high tone stimulus.
4. Tuning fork tests: The Rinne and Weber tuning fork tests serve to distinguish between a conduction defect and a perception disorder (inner ear disorder or neurosensory hearing loss).

5. Postural tests: Balance tests such as Romberg's test. The "stork" variant - standing on one leg gives more information.
6. Tests for nystagmus - Gaze test: Have the patient look at point 30° away from the median line to the right and left in succession. (a) Latent nystagmus becomes stronger when looking in one direction and not dying away. Cause: Peripheral vestibular disorder. (b) Nystagmus appearing exclusively when looking to one side - Unilateral gaze nystagmus. Cause - Central disorder of the nervous system. (c) Nystagmus both when looking to the right and looking to the left (symmetrical gaze nystagmus). Cause - Disorder of CNS drug abuse.

Localizing features

- Inner ear: hearing loss, tinnitus, aural fullness, otalgia or otorrhoea
- VIII nerve: facial weakness
- Cerebellopontine angle: impaired facial sensation, clumsiness, dysarthria, dysphagia, cranial nerve palsies, hemisensory loss, hemiparesis or memory disturbances
- Cerebellum: incoordination, clumsiness, dysarthria
- Cortex: Loss of consciousness, olfactory or gustatory hallucinations

Duration of vertigo – possible causes

- A few minutes: BPPV, vestibular epilepsy
- Several minutes to <2 hours: benign recurrent vertigo, vestibular aura of migraine
- 2 hours to <24 hours: Meniere's disease, transient ischemic attack in the posterior circulation
- >24 hours: acute peripheral vestibular dysfunction, relapse of brainstem multiple sclerosis, bilateral vestibular failure.

TYPES OF VERTIGO

Table 2 gives types of vertigo.

Table 2: Types of vertigo

Paroxysmal vertigo
Sudden attack which lasts for only a short time and then goes away quickly.
Single severe attack of vertigo
The attack which does not disappear quickly but only diminishes slowly in the course of days or weeks and disappears spontaneously.
Chronic vertigo
Often not serious but with small flare ups permanently present. Lasts months without any change.

Contd...

Contd...

Positioning vertigo
Occurs following sudden movement of the head, often in one particular plane.
Dizziness spells
More prevalent among older people.

Syndromes

1. *Benign positional paroxysmal vertigo* – Vertigo occurs when a person lies down in a particular way. The vertigo appears after a latent period of a few seconds, lasts not more than 30 seconds and quickly fades. The cause is assumed to come from debris in the endolymph of the posterior canal. *Tr.* Adaptation exercises (Epley's maneuver).
2. *Meniere's syndrome* – Attacks of vertigo lasting minutes or hours, accompanied by tinnitus in one ear and varying but gradually worsening hearing loss in that ear. The syndrome occurs with various internal disorders and also as an independent disorder, when it is called Meniere's disease. *Tr.* Pharmacotherapy, in severe cases surgery can be considered.
3. *Unilateral vestibular disease syndrome* (acute vestibular vertigo) caused by sudden loss of labyrinthine function. Vertigo is severe at the onset but fades away slowly over 2 or 4 weeks.
4. *Hyperventilation* can cause reduced CO_2 tension in the blood which can lead to cerebral ischemia. This can manifest itself in visual disturbances. Dizziness in the form of giddiness often reported. Anxiety and tachy cardia. Hyperventilation can result from stress situations. *Tr.* - Counselling. Advising patient to breath into a bag in front of the head in the event of an attack, and sedative medication if necessary.
5. *Juvenile vertigo* occurs in children between ages of 4 and 14 and involves attacks lasting a few seconds or minutes during which the most pronounced symptom is anxiety. The syndrome disappears spontaneously within a few months to few years. *Tr.* - Low dose antiepileptic if frequency of attack is >once a week.
6. *Senile vertigo* can occur in patient over age of 65. Cerebral atherosclerosis plays a major role. *Tr.* - Pharmacotherapy, avoiding drugs which cause drowsiness.
7. *Vestibular neuritis* mostly follows infection of upper respiratory tracts. The condition clears up within 3–6 weeks, without any persistent loss of ear function.
8. *Migraine:* Vertigo sometimes occurs as a side effect of migraine. Specific therapy to control the vertigo is only rarely needed.

MANAGEMENT

1. ***Pharmacotherapy*** – (a) For symptoms of acute episode antiemetic like prochlorperazine 5 mg mouth dissolving tablet. (b) Vestibular sedatives – Betahistine 60 mg/day, Cinnarizine 50-255 mg/day. (c) Piracetam may be effective in older patients 400–800 mg tds. (d) Sulpiride 50 mg tds. (e) Diazepam 10–20 mg/d in combination with a drug with more specific action to reduce severity of an attack.
2. ***Adaptation methods.*** BPPV in particular responds well to this treatment. Exercises –
   a. *In bed:* (i) Eye movements. Looking up and down. (ii) Looking alternately left and right. (iii) Convergence exercises. (iv) Head movements. (v) Bending alternately forward and backward.
   b. *Sitting:* (i) Shrugging and rotating shoulder. (ii) Bending forwards and picking objects from the floor. (iii) Turning head and trunk alternately to the left and right.
   c. *Standing:* (i) Changing from sitting to standing, first with eyes open, then with eyes shut. (ii) Throwing a small (ping pong) ball in an arc from hand to hand and following it with the eyes.
   d. *Walking*: (i) Throwing and catching a ball while walking. (ii) Walking around the room with eyes opened and closed. (iii) Walking up and down a flight of stairs.
3. ***Surgery.*** This involves severing one vestibular nerve or destroying one inner ear in the case of chronic perilabyrinthitis or a seriously disabling form of unilateral Meniere's disease.

   The application of gentamy cin into the middle ear in severe forms of Meniere's disease has shown good results.

4. ***Physical therapy***

Peripheral vestibular dysfunction – when vertigo continues to recur after an acute peripheral vestibular episode, the patient is described as 'poorly compensated'. Central compensation is expedited by balance exercises.

BPPV – Particle repositioning manoeuvres (e.g. Epley) achieve a cure in up to 70% patients. Recurrent BPPV can be treated by Brandt-Daroff exercises.

Central vestibular disorders – Eye movement disorders that cause oscillopsia can be managed with low dose clonazepam or baclofen.

Cognitive behavioural therapy. Avoidance behaviour seen in patients with protracted vertigo or dizziness may require desensitization programmes by a therapist. Cognitive therapy may be required in more complex cases in which there is an inappropriate focus on the vestibular symptoms or when illness behaviour has developed.

3. SYNCOPE

A transient sudden loss of consciousness and postural tone due to acute decrease in cerebral blood flow. It is the most common non-epileptic cause of loss of consciousness.

CAUSES

A. Syncope due to decrease of cerebral blood flow (Neural syncope)

1. ***Vasomotor syncope***

   Vasovagal syncope (Common faint) – In susceptible individuals emotional and physical stimuli such as fright, pain and unpleasant sights, exhaustion, hot atmosphere, long period of standing in same position may produce syncope. The patient appears pale, there is usually slow pulse, low blood pressure and dilated pupils.

   Carotid sinus syndrome – Attacks of unconsciousness result from hypersensitivity of carotid sinus, and occur most frequently in elderly and in association with hypertension and arteriosclerosis. Mild pressure over the carotid sinus, e.g. by tight collar combined with head turning causes bradycardia, hypotension and occasionally transient asystole lasting 10–15 seconds.
2. ***Postural syncope*** – as a result of failure of baroreceptors which normally adjust heart rate and peripheral resistance in response to change of posture. *Causes* – (a) Arising abruptly from a prolonged period in recumbent position often causes giddiness and syncope particularly in presence of cerebral vascular insufficiency. (b) Following strenuous physical exercise. (c) Chronic orthostatic hypotension may result in giddiness or syncope or both following a decline of systolic pressure usually at least 30 mm Hg. when the patient remains stationary in the upright position. (d) In association with neurologic disorders such as diabetes mellitus and other forms of polyneuritis and patients receiving drugs such as phenothiazines. Parkinson's disease especially in elderly patients treated with L-dopa.
3. ***Cerebral syncope*** – Syncope may be a consequence of direct brain damage secondary to trauma or associated with carotid or vertebrobasilar disease. Recurrent attacks of syncope more in the erect posture. In subclavian steal syndrome exercise of the involved arm is followed by syncope.
4. ***Situational syncope***
   a. *Cough (and sneeze) syncope* – may occur after paroxysms of cough especially in patients with bronchitis and emphysema and is caused by increase in intrathoracic pressure which occurs with coughing and impedes venous return to the heart.

b. *Micturition syncope* – may occur in men with lower urinary tract obstruction straining excessively to pass urine usually at night. Due to postural fall in B.P., reflex vagal activity stimulated by a full bladder, and reduced venous return caused by straining.

c. *Basilar artery migraine* – may cause transient loss of consciousness and is usually encountered in children with history of severe occipital headache.

B. **Syncope due to inadequate stroke volume (Cardiac syncope)**

1. ***Cardiovascular***
   - Obstruction to LV outflow – AS, hypertrophic cardiomyopathy, LA myxoma, mitral stenosis.
   - Obstruction to pulmonary flow – PS, pulmonary hypertension, pulmonary embolism, tetralogy of Fallot, RA myxoma.
   - Cardiac tamponade
   - Aortic dissection
   - Arrhythmias – (a) Bradyarrhythmias: Sick sinus syndrome, 2nd and 3rd degree AV block, pacemaker malfunction. (b) Tachyarrhythmias – SVT, VT.
2. ***Reflex syncope*** – Cardiac standstill occurring from reflex vagal activity, e.g. following distension of viscera, fainting associated with irritation of pleura or peritoneum, cardiac asystole associated with oesophagoscopy or bronchoscopy, and in glossopharyngeal neuralgia and cardiospasm, and pathological lesions in larynx and mediastinum.

C. **Syncope due to metabolic causes**

1. ***Hypoxia*** – Oxygen lack may occur at high altitudes or at lower levels of altitude in patients with aortic stenosis, congenital heart disease, pulmonary hypertension or anemia. There may be cyanosis at onset of impairment of consciousness followed by convulsions. In some subjects, breathing gas mixture with a low O_2 content can precipitate syncope. It is also one of the factors which may precipitate syncope during administration of nitrous oxide for dental procedures.
2. ***Hypoglycemia*** – in diabetic patient, or spontaneous due to insulin secreting tumour of pancreas. Tendency to occur after prolonged period of starvation. Associated with profuse sweating, prompt relief after glucose.
3. ***Hyperventilation*** – may induce respiratory alkalosis which can predispose to syncope.

D. **Hysterical syncope** – Loss of consciousness of psychologic origin. No alteration of pulse or blood pressure.

E. **Orthostatic syncope** - defined as a reduction in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 min of standing or head-up tilt on a tilt table, a manifestation of sympathetic vasoconstrictor (autonomic) failure (Table 3).

Management – (a) *Vasovagal attacks and syncope in general* – Immediate treatment is to place the patient at once in recumbent position in order to restore sufficient B.P. for cerebral perfusion to be resumed. (b) *Cough syncope* – Vigorous treatment of chest condition with antibiotics and antitussive drugs. (c) *Micturition syncope* – Patient on waking at night must be advised to sit on edge of the bed for a short period before going to lavatory. He should be encouraged to micturate in the sitting position. (d) *Carotid sinus syndrome* – Anticholinergic drugs or if this fails surgical denervation of carotid sinus (nerve of Herring). (e) *Postural hypotension* – Elevation of foot of bed, elasticated stockings. Mineralocorticoid fludrocortisone, indomethacin, sympathomimetic drugs or cardiac pacing may be indicated.

4. NUTRITION

DIETARY REQUIREMENTS

Energy intakes: The total energy intakes and needs of individuals of same age, sex and weight with differing levels of physical activity vary by plus or minus 30%, individuals

Table 3: Causes of orthostatic syncope

1. Neurodegenerative diseases—the "Synucleinopathies" – Lewy body diseases – Parkinson's disease – Lewy body dementia – Pure autonomic failure – Multiple system atrophy (the Shy-Drager syndrome)
2. Secondary autonomic failure due to autonomic peripheral neuropathies – Diabetes – Hereditary amyloidosis (familial amyloid polyneuropathy) – Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated) – Hereditary sensory and autonomic neuropathies (HSAN) (especially type II-familial dysautonomia) – Idiopathic immune-mediated autonomic neuropathy – Autoimmune autonomic ganglionopathy – Sjogren's syndrome – Paraneoplastic autonomic neuropathy – HIV neuropathy – Postprandial hypotension – Iatrogenic (drug-induced) – Volume depletion

appetites are geared to their energy needs. As adults age, they become progressively less active and lose lean tissues, including muscle, thereby reducing their BMR as well as energy expended in activity.

Foods – The consumption of appropriate mix of different foods, vitamins and minerals is necessary to avoid deficiency diseases. However, many diseases such as obesity, diabetes, heart disease, hypertension, gallstones and some cancers have a substantial nutritional component.

Proteins – for growth and repair. To maintain nitrogen balance 40–50 g of protein/day are needed. The amount of nitrogen excreted in urine represents the balance between protein breakdown and synthesis. The amount of absorbed protein retained by the body determines the biological value of protein, and this depends on the amount of essential amino acids present. Milk and eggs have high biological values, and plants such as maize and beans low values.

Carbohydrates – Carbohydrates and fats form energy foods. Carbohydrates can be consumed in the form of whole grain cereals, wholemeal bread, chapattis, pasta and rice, potatoes, peas, beans, lentils, vegetables and fruits. Intake of starchy foods provides sources of fibre, minerals and vitamins, and provides a beneficial replacement for high fat foods. Cereal fibre protects against constipation, other bowel disorders and, perhaps, bowel cancer. It may also protect against gallstones by modifying the recycling of bile salts. Soluble fibre (e.g. in fruits and vegetables) also reduces plasma cholesterol levels. Starchy foods may benefit diabetics by allowing a slower release of glucose into the blood and reduction in demand for insulin.

Fat – Guidelines for reducing total and saturated fat intake – (a) Semi-skimmed milk for older children and adults, full-cream milk for children under 5. (b) Potatoes as baked, boiled, mashed or as grilled croquettes, not fried or roast. Fresh fruits, perhaps with plain yogurt (curds), instead of ice creams, puddings, or cream cakes, biscuits and chocolates. Cheese of lower fat variety if at all. Low fat butter or margarine which is high in polyunsaturated fats and has same calories as butter. White fish is low in fat. Oily fish such as sardines, salmon, herring contain polyunsaturated oils, which may reduce cholesterol levels. Lean meat, avoiding frying. Avoid sausages, pies and pastas and most processed meats. Choose cooking oils of corn, soya, linseed, rape, sunflower, olive or safflower oils. Linoleic acid, the essential fatty acid, occurs naturally in whole grain cereal, seeds and nuts.

NUTRITIONAL DISORDERS

Obesity: has been defined as the weight-for-height above which there is increased mortality and has been discussed in the Chapter on Endocrine diseases.

Undernutrition: Optimal nutrition is necessary for optimal health, but neither variables can be measured accurately; thus it is difficult to define undernutrition. In adults weight loss is used as a simple index. In children, growth and development are sensitive markers of nutritional state, but the range of normality is considerable.

Causes of Undernutrition

1. Starvation or famine.
2. Reduced food intake for psychological reasons (e.g. anorexia nervosa).
3. Intestinal disorders leading to anorexia and/or malnutrition.
4. Severe pathology of any kind (e.g. infection, inflammatory and neoplastic disorders, and organ failure) which may lead to anorexia and enhanced catabolism.

Under all these circumstances, there is loss of body fat and wasting of skeletal muscle with variable degrees of atrophy of body viscera except the brain. The degree of wasting of individual components varies with the disease process and other factors such as age, sex, physical activity, adequacy of intake of specific nutrients and the patient's hormonal status.

Malnutrition and undernutrition in children have been described in Chapter on Diseases of Children.

Undernutrition in adults

Medical history: Indicators for risk of malnutrition include –

- Loss of weight (recent or past)
- Anorexia and loss of appetite
- Nausea and recurrent vomiting
- Recurrent diarrhoea
- Weakness, lassitude and reduced physical activity
- Recurrent fever and infection
- Recent surgery or trauma
- Drugs or medications
- Recent bereavement or social stress
- Physical disability (e.g. blindness, arthritis)

Dietary history: Daily food and nutrient intake, pattern of meals, alcohol and food fads.

General appearance – of the patient should indicate the size of subcutaneous fat stores and degree of hydration. Vitamin and mineral deficiencies indicated by pallor,

skin lesions and pigmentation. Skeletal muscle wasting is demonstrated by appearance of temporalis and periscapular muscles and by circumference of mid-upper arm. Recent unintentional weight loss of >10%, body wt. <80% of the desirable wt. for height and body mass index (BMI) <18.5 kg/m^2 are useful indices for undernutrition and malnutrition.

Investigations and Specific Nutritional Tests

Laboratory investigations:

- Haemoglobin or packed cell volume (anemia, hydration)
- Blood urea (hydration, protein intake)
- Dystrophy of skin and mucous membranes
- Oedema
- Reduced cardiac size
- Enlarged liver, possibly caused by fatty infiltration
- Muscle weakness disproportionate to muscle wasting
- Altered mental state

Examination may show nutrition– related disorders:

- Plasma proteins
- Acute-phase proteins – C-reactive protein and ESR (inflammatory or neoplastic pathology)
- Creatinine excretion (muscle mass)
- Short half-life nutritional proteins (e.g. transferrin, retinol-binding protein) help assess response to repletion but are also affected by inflammation.
- Total lymphocyte count (immune function)

Specific tests that can be used as bedside to assess altered nutritional status:

- Tests of muscle function (e.g. grip strength and voluntary muscle contraction using hand-grip dynamometry)
- Changes in force-frequency curve obtained by stimulating ulnar nerve at the wrist and measuring contraction and relaxation rate of adductor pollicis muscle
- Estimation of daily urinary nitrogen excretion to assess protein catabolism (use of this technique is limited by need for 24-hr urine collection).

BMI is a simple, reliable and easily obtainable measure of nutritional status in adults. It is reasonably highly correlated with body fat, (a proxy for available body energy stores) and is relatively independent of stature or height. It is obtained by dividing weight (in kilograms) by height (in meters) squared. BMI <18.5 kg/m^2 in adults indicates chronic undernutrition. Three grades of severity of adult undernutrition (FAO/2 WHO):

- Grade I – BMI 17–18.49 kg/m^2
- Grade II – BMI 16–16.99/m^2
- Grade III – BMI <16kg/m^2

Nutritional Effects of Disease

Cancer cachexia – Wt. loss is a common problem in cancer patients; cancer treatments sometimes contribute to it. Patients with solid tumors are more commonly affected than those with haematological malignancies.

Endocrine disorders – (a) Diabetes: Wt. loss is a common presenting feature of type 2 diabetes and insulin therapy in both type 1 and type 2 disease results in wt. gain. (b) Hyperthyroidism. (c) Addison's disease.

Respiratory disorders

Cystic fibrosis: Potential causes of malnutrition are – malabsorption due to pancreatic insufficiency, reduced food intake due to gastro-oesophageal reflux, state of wasting associated with lung disease, occasionally a distal intestinal obstructive syndrome resulting from underlying lung disease or injudicious use of pancreatic supplements.

COPD: Factors contributing to the state of negative energy balance – Increased energy costs of breathing, metabolic costs of respiratory tract infections, breathlessness caused by act of eating, hyperinflation of the lungs causing extrinsic pressure on the stomach that results in a feeling of satiety at lower levels of food intake, and thermogenesis induced by diet and drugs (theophyllines, β-agonists).

Cardiac cachexia: The underlying mechanisms are unclear, but perturbations of neuroendocrine and immunological homeostasis driven by tissue hypoxia appear to mediate. Drug-induced side effects (e.g. anorexia with digoxin, altered taste with some ACEIs) may also contribute.

Rheumatoid arthritis and connective tissue disease: Reduced peripheral action of insulin, caused by tumour necrosis factor a (TNF-α)-driven disruption of insulin receptor signalling, may have a role in muscle wasting in RA and other connective tissue diseases. Muscle wasting is aggravated by reduced muscle activity and ensuing 'disuse atrophy'.

Chronic kidney failure: Under normal circumstances, the body responds to a low-protein diet by suppressing protein and essential amino acid degradation. Protein metabolism in uremic patients is characterized by a perturbation of this normal response, resulting in negative nitrogen balance and loss of lean body mass. Metabolic acidosis and low insulin concentration contribute to compound this state of negative nitrogen balance.

HIV and tuberculosis: Protozoal, bacterial and viral GI infections and sometimes side effects of HAART contribute to poor nutritional status. HIV enteropathy is a cause of malabsorption and wt. loss in absence of any demonstrable infection in the gut. Other nutrition derangements associated with HIV include hyperlipidemia and syndrome X (insulin resistance), and protease inhibitor therapy is associated with a lipodystrophy syndrome.

Stroke: Poor nutritional status remains a potentially remediable cause of poor outcome in stroke.

ARTIFICIAL NUTRITIONAL SUPPORT

Enteral Nutrition

Enteral nutrition is simple, cheaper, associated with improved immune function and carries a lower risk of bacterial translocation. Supplemental tube feeding is preferred in patients who are unable to take sufficient nutrition orally. In some (e.g. those with swallowing difficulty), all nutrition must be given artificially.

Access – *Nasoenteric tube-feeding* is an excellent short-term solution. Nasojejunal feeding is necessary when gastric emptying is impaired, but may also help to reduce aspiration and diarrhoea.

Pre-albumin — A marker of malnutrition

Due to very long half-life of albumin (21 days), it is not considered a very good indicator of serum loss. This means that though there is a severe loss, albumin level remains elevated, because of its transcapillary escape into interstitial fluid. This escape is markedly increased in systemic inflammatory response syndrome. Prealbumin is more sensitive to protein energy status than albumin and its levels indicate recent dietary status rather than overall nutritional value.

Interpretation of Prealbumin Test

• Level	Risk of malnutrition
• <100 mg/L	Severe
• 100–170 mg/L	Moderate
• >170 mg/L	No risk

Prealbumin measurements is very useful in patients undergoing major surgeries.

Assessing nutritional requirements

Standard equations such as Harris Benedict equation based on height, weight, age and sex can be used to estimate the Basal Energy Expenditure (BEE).

a. **For male**

BEE (kcal/day) = 66 + (13.7 × weight) + (5.0 × weight) - (6.7 × age)

b. **For female**

BEE (kcal/day) = 65.5 + (9.6 × weight) + (1.8 × weight) - (4.7 × age)

Weight in kg, height in cm and age in years.

This equation however does not take into account the stress factor which is important in critically ill patients. To simplify one can calculate daily needs from 25–30 kacl/kg/day.

Essentials of prescribing nutrition: (i) Energy – Main substrates providing energy are carbohydrates and lipids. Glucose should constitute 0.80% of non-protein calories. Proteins – In critically ill patients 1–1.5 kg/day is recommended. (ii) Micronutrients, vitamins and trace elements. Enteral nutrition intrinsically has adequate supply of micronutrients but parenteral administration requires both vitamins and micronutrients.

Types of feed – Standard feeds may be divided into two main categories: (a) *Whole-protein feeds* in which the protein source is not pre-digested and is derived from milk hydrolysed casein or soya protein. Carbohydrate is provided as maltodextrins, glucose, sucrose or corn syrup solids. Fat source is usually a vegetable oil derivative, but other fat sources incorporate a re-blending of monounsaturated or polyunsaturated fatty acids from rapeseed and fish oils. *(b) Elemental/peptide feeds* – Here the nitrogen source is free amino acids or peptides. Pre-digested feeds may be used in patients with absorption difficulties (e.g. pancreatitis, Crohn's disease).

Most standard feeds provide 1 kcal/mL; other feeds are energy dense, providing 1.2–2 kcal/mL Fibre-containing feeds are used for long-term feeding, because they are thought to normalize gut bacteria and transit time. Feeds are also developed for use in particular situations:

- Low sodium, potassium and phosphate for kidney failure
- High fat for respiratory failure (the higher respiratory quotient of fat reduces carbon dioxide production, which is of theoretical benefit in patients with CO_2 retention)
- Branched-chain amino acids for chronic liver disease (said to normalize blood amino acid profile)
- Immuno-enhancing for critical illness (arginine, mega-3 fatty acids and immune glutamine can enhance function).

Parenteral Nutrition

Administration of PN has been simplified due to the availability of ready to use all-in-one (mix of carbohydrates, lipids and protein) bags which assure less handling and thereby less infection.

Indications

(a) Intestinal failure (e.g. ileus, intestinal obstruction, short bowel syndrome and severe mucositis resulting from chemotherapy), which is analogous to failure of other end organs such as the kidney, heart and endocrine glands. (b) When GI tract has to be rested, e.g. to allow a GI fistula to heal or to prevent pancreatic stimulation after severe and recurrent pancreatitis.

Access

Vascular access can be obtained peripherally or centrally. Peripheral access is used only for short-term, low osmotic load feeding, and require good peripheral veins. A small cannula should be placed into a large vein away from a joint using sterile technique. Central venous cannulation is necessary for long-term parenteral nutrition with hyperosmolar feeds. Narrow-bone silicon lines enable peripheral access to veins but more central feed delivery from the tip of the line (PICC lines).

Feed Delivery

Most feeds are delivered continuously over 24 hours in patients who are acutely unwell. A period without feeding during each 24 hours is thought to reduce liver dysfunction.

Factors which impair the administration of internal feeds in a critically ill patient - (a) Gut hypomotility. (b) Hemodynamic instability. (c) The feeds need interruption for procedures and surgeries in the ICU.

Problems with parenteral feeding

1. *Overadministration of trace elements* – IV administration of feeds has important metabolic and nutritional consequences. The GI tract normally acts as an important defence 'organ' against trace element toxicity. It is inappropriate and sometimes dangerous to administer the same quantities of micronutrients I.V. as orally.
2. *Underadministration of some amino acids* – Certain amino acids (e.g. tyrosine, cysteine, glutamine) are not present in I.V. feeds because they are poorly soluble or unstable. If amino acids are deficient, protein synthesis may be limited.
3. *Bypassing the liver* – IV administration bypasses the liver, an obligatory route by which nutrients enter the body during enteral feeding.
4. *Disuse atrophy* – may follow prolonged parenteral nutrition.

Nutrient Requirements

Protein (nitrogen N) requirements – also vary with age, degree of malnutrition and disease activity, but an intake of 11–16 g N is adequate for most adult patients. It is seldom necessary to restrict intake to less than 9 g N/day in (equivalent to approximately 125–155 g protein/day).

Fluids – Fluid restriction may be necessary in presence of cardiac, hepatic or renal failure, and in patients with recent head injury, who may have raised intracranial pressure. In contrast excess fluid must be given to patients with large GI fluid losses, e.g. patients with high output fistulas or large nasogastric aspirates.

Vitamins – In contrast to many trace elements, the requirements of vitamins are substantial, because patients receiving i.v. nutrition often suffer from severe systemic disease. Pharmacological doses of antioxidant Vitamin A, C and E may neutralize or prevent the damaging effects of free radicals, found in excess in many disease states.

Other pharmacological agents – (a) Growth hormone (GH) and insulin-like growth factor given to catabolic patients to improve nitrogen balance and perhaps muscle strength. In some patients with respiratory disease, GH may improve respiratory m. function. (b) Recombinant human erythropoietin in end-stage kidney failure eliminates associated anemia and requirement for blood transfusions.

VITAMIN AND TRACE ELEMENT DEFICIENCY

Immunonutrition:

Glutamic acid is an amino acid which is synthesized by all tissues. It is essential for maintenance of gut metabolism structure and function and also promotes lymphocyte activation enhancing the immune system.

5. ANTIOXIDANTS

Oxidative damage from both endogenous sources and exogenous sources (e.g. smoking, ionizing radiation, ultraviolet light), is involved in the development of many diseases.

Antioxidant defence system. Antioxidants are substances that, when present at much lower concentrations than a vulnerable oxidizable substrate, significantly delay or prevent its oxidation.

- Vitamin E protects lipids in cell membranes and organelles from oxidation.
- Vitamin C scavenges reactive oxygen species and possibly regenerates vitamin E in the tissues.
- Carotenoids (e.g. β-carotene) can scavenge radicals under physiological conditions and are potent scavengers of singlet oxygen.

In addition, several enzymes with antioxidant function require trace elements such as selenium, copper, zinc, manganese and iron as co-factors.

Table 4: Sources and requirements of vitamins

Food sources, daily requirement	*Symptoms and signs of deficiency and toxicity (if any)*
Fat soluble vitamins	
Vitamin A Animal: Milk, butter, liver and fish liver oils, egg yolk Vegetable: (carotene precursors) carrots, sweet, potatoes, apricots, spinach. • Mango, papaya • 5,000 IU (1.5 mg vitamin A) • 5,000 IU/kg body weight/day • Plasma vitamin A low • (<1 µmol/litre)	*Skin* • Asteatosis is earliest manifestation • Phrynoderma (toad skin). Brown to dark brown, dry, rough, hyperkeratotic follicular papules with central keratotic horny spurs. Bilateral and symmetrical distribution in anterolateral aspects of thighs, posterolateral aspects of arms. • In severe cases the follicular papules develop in entire upper and lower extremities, shoulders, abdomen, buttocks, face and back of neck. *Eyes* • Nyctalopia (earliest symptom) • Hemeralopia: inability to see bright light • Xerophthalmia: includes one or more of the following changes – Conjunctival xerosis – Bitot's spots (keratinizing epithelium) forming greyish-white triangular plaques on conjunctival surface lateral to the cornea. – Corneal xerosis – Corneal ulceration with xerosis – Keratomalacia • *Teeth:* Impaired enamel formation • *Acute toxicity* (massive single dose) – Abdominal pain, nausea, vomiting, headache, dizziness followed by generalized desquamation of skin. • *Chronic poisoning* – Bone and joint pains, loss of hair, fissuring of lips, anorexia, benign intracranial hypertension, weight loss, hepatomegaly. • *Carotinaemia* – is due to excessive consumption of vitamin A precursors in food, mainly carrots. Yellowing of skin maximum in palms and soles.
Vitamin D Fish liver oil, milk, egg yolk, butter, yeast. Synthesis in the skin when it is irradiated. 400 IU (IU = 0.025 mg vitamin D_2) 5,000 IU/day Plasma 25-hydroxychloecalciferol is a good indicator of vitamin status. Low plasma calcium	Tetany and rickets in infants and children Osteomalacia in adults *Toxicity* – Anorexia, lassitude, vomiting, diarrhoea, profuse sweating, polyuria, polydipsia and headache. Hypercalcemia causes calcium deposition in tissues and kidneys which may lead to renal failure.
Vitamin E Alfalfa, wheat germ oil, lettuce, maize, molasses, peas, whole rice, meat, milk, eggs. 8 mg/day tocopherol equivalents 100–600 mg/day Plasma vitamin E concentrate533 Resistance of RBC to haemolysis by hydrogen peroxide	Skin: Erythematous papular eruptions, oedema and flaky dermatitis Anemia in premature infants In chronic deficiency: ataxia, posterior column dysfunction, peripheral neuropathy and visual scotoma Vitamin E deficiency usually develops in premature infants, adults with fat malabsorption syndrome or individuals with genetic anomalies in transport proteins. In severe vitamin E deficiency - Acanthocytosis of red cells, and thrombocytosis. Ophthalmoplegic and pigmentary retinopathy. Posterior column and spinocerebellar tracts may be involved.
Vitamin K Green vegetables, spinach, cabbage, egg yolk, cheese, tomatoes. K1 synthesised by bacteria in intestines Adult daily requirement 2 mg Prolonged prothrombin time	Hypoprothrombinaemia with defective coagulation of blood Skin: Intracutaneous haemorrhages, purpura and ecchymosis.

Contd...

Contd...

Food sources, daily requirement	*Symptoms and signs of deficiency and toxicity (if any)*
Water soluble vitamins **Vitamin B complex** ***Vitamin B$_1$*** (Thiamine) Yeast, meat, whole grain cereals, beans, liver, egg yolk, potatoes. (Synthesised by micro-organisms). 1–1.5 mg 50–100 mg Measurement of RBC transketolase activity, with addition of thiamine pyrophosphate. Elevated blood pyruvate. Blood or urine measurement of thiamine. ***Vitamin B$_2$*** (Riboflavin) Milk, eggs, liver, germinating seeds 2 mg 5–10 mg RBC glutathione reductase activity with addition of flavin adenine dinucleotide (high degree of activation of enzyme activity indicates deficiency). Low urinary riboflavin concentration.	*Wet beriberi* Cardio-vascular beriberi is commonly a high output biventricular failure, which is preceded by sinus tachycardia, wide pulse pressure, and severe sweating. Low-output cardiac failure (e.g. Shoshin beriberi). *Dry beriberi* Neurological features – Peripheral neuropathy, ataxia, amblyopia and burning paraesthesia (e.g. burning mouth syndrome). Wernicke's encephalopathy – Korsakoff's syndrome Lactic acidosis Angular stomatitis, perleche Cheilosis with erythema, xerosis and vertical fissuring of the lips Glossitis with smooth magenta red tongue and enlarged fungiform papillae Cutaneous: Seborrheic-dermatitis-like rash affecting naso-labial folds, alae nasi, nasal bridge, forehead, cheeks, postauricular regions, eyelids, scrotum and vulva. These areas appear red, greasy and sometimes hyperpigmented (scar skin or dyssebacia) Eyes: Neovascularization of cornea and epithelial keratitis resulting in photophobia and lacrimation Potentiation of oral anticoagulants (due to inhibition of prothrombin time) In premature children – Hepatosplenomegaly, ascites, cholestatic jaundice, and thrombocytopenia. Jaundice in the new born if given during pregnancy. Weakness and fatigue occur early
Nicotinic acid (PP factor) Liver, eggs, yeast, meat, rice, fish, whole grain 20 mg 500 mg (Requirement does not increase during pregnancy)	*Cutaneous* Acute onset with appearance of well demarcated patches of erythema with pruritus, burning, resembling sunburn, symmetrically on exposed areas such as back of hands and forearms, face and neck, upper central part of chest, knees and dorsum of feet depending on pattern of clothing used. Intertrigo with redness and maceration may occur in intertriginous areas. Chronic – The patches turn reddish brown, rough and scaly, thickened and pigmented. Desquamation occurs after several weeks or months leaving areas of hypopigmentation. The sharply demarcated lesions on upper central parts of chest and neck form the Casal's necklace. On the face, there is a dull-red erythema on bridge of nose and adjacent areas on the cheeks with powdery scaling (butterfly erythema and pigmentation). *Mucous membranes.* Cheilosis with furrowed lips, angular stomatitis. The tip and margins of the tongue and oral mucosa, including gingival mucosa become inflamed, swollen, ulcerated and assume a bright scarlet colour. *GI system* – Anorexia, dyspepsia, nausea, vomiting and abdominal pain may occur. Diarrhoea, often bloody if GI hyperaemia is severe. *CNS* – Neuropsychiatric manifestations including impairment of memory, apathy, depression, psychosis and coma may develop. Encephalopathic syndrome may occur. Neonatal form may present as crusted or fiery red dermatitis, while the infantile form resembles acrodermatitis enteropathica.
Vitamin B$_6$ (Pyridoxine) Yeast, liver, meat, cereals, milk, eggs, lettuce, spinach 2 mg 50-100 mg Estimates of deficiency – (a) Loading tests – measurement of urinary tryptophan metabolite after tryptophan loading or cystathionine assessment after methionine load. (b) Measurement of N-methylnicotinamide in urine.	Paranasal erythema, seborrheic-like rashes on face, scalp, neck, shoulders, buttocks and perineum, intertrigo and pellagra-like dermatitis. Cheilosis, angular stomatitis, glossitis, flattened filiform papillae, and ulcerations may occur. Peripheral neuropathy from isoniazid therapy for TB. Somnolence, confusion, and in infants convulsions can occur. *Contraindications for pyridoxine* – 1. Along with L-dopa therapy. 2. Lactating mothers.

Contd...

Contd...

Food sources, daily requirement	*Symptoms and signs of deficiency and toxicity (if any)*
(c) Measurement of RBC transaminase activity with addition of pyridoxine supplements (Activation of enzyme activity of <150% is regarded as normal).	*Uses of pyridoxine* – 1. With INH, D-penicillamine, cycloserine, hydralazine, oral contraceptives. 2. Alcoholism. 3. Hyperemesis gravidarum. 4. Radiation sickness and motion sickness. 5. Sideroblastic anemia. 6. Infantile convulsions. 7. Homocystinuria. 8. Hyperoxaluria. 9. Hartnup disease. 10. Local application in dry seborrheic dermatitis. *Toxicity* – Severe peripheral neuropathy with ataxia, perioral numbness, loss of vibration sense. No sensory loss, no diminished reflexes.
Pantothenic acid Liver, kidney, eggs, meat, whole grain and milk 10 mg.	Deficiency occurs with other vitamin deficiencies and protein-energy malnutrition
Biotin (Anti-egg white factor) Liver, eggs, meat 4–7 mg. 10 mg.	Dermatological features: Xerosis, generalized pallor, intertriginous and periorifacial dermatitis, fine bran-like scaling and alopecia. Also atrophic glossitis, brittle nails. Two inherited forms of deficiency (both AR) 1. Neonatal deficiency, more severe of the two, caused by lack of enzyme monocarboxylase synthetase seen in infants in first 6 weeks of life. Infantile biotin deficiency occurring after 3 months of life is due to deficiency of enzyme biotinidase. 2. Dermatological features in adults: Xerosis, generalized pallor, intertriginous and perioral dermatitis, fine bran-like scaling alopecia. Atrophic glossitis and brittle nails are other features. Neonatal form may present as a crusted fiery red dermatitis. Infantile form resembles acrodermatitis enteropathica.
Choline Egg yolk, liver, meat Therapeutic dose 3–6 gm.	Fatty liver and cirrhosis. Haemorrhagic renal lesions, vascular congestion and tubular degeneration.
Folic acid Yeast, fresh green vegetables, liver, kidney, cereals, meat 0.15 mg daily	Megaloblastic anemia, glossitis, stomatitis, diarrhoea.
Vitamin B_{12} (Cyanocobalamin) Liver, kidney, eggs, milk. 2.5 µg	Megaloblastic anemia, neuropathy, anorexia, diarrhoea, ataxia, optic neuritis, mental changes
Vitamin C Green vegetables, fruits especially citrus, black currants and strawberries, potatoes 30 mg., double in pregnancy Adult 100 mg qds. Children under one year: 25 mg. qds. Plasma concentration of ascorbic acid (indicates recent intake). Measurement of leucocyte vitamin C.	*Scurvy:* Hyperkeratotic hair follicles with perifollicular haemorrhages Petechiae and ecchymosis may occur on any part of body, but more commonly on areas subjected to even minor trauma or pressure. Feet and ankles are involved early (woody legs). Subconjunctival, subungual, subcutaneous, subperiosteal and intra-articular haemorrhages may occur. Follicular hyperkeratosis is seen on anterior aspects of forearm, abdomen and posterior aspects of thighs. Corkscrew hair (due to reduced disulphide bonds) are seen. Gingival hypertrophy with enlarged submandibular salivary glands and Sjogren-like syndrome may occur. Delayed wound healing. Microcytic, normochromic, or macrocytic anemia *Uses of vitamin C* – Scurvy, wound healing, common cold, methemoglobinaemia, alkaptonuria, acidification of urine, along with iron therapy, haemorrhagic disease of newborn, correction of leucocyte abnormalities in Chediak-Higashi syndrome, atherosclerosis.

Contd...

Contd...

Food sources, daily requirement	*Symptoms and signs of deficiency and toxicity (if any)*
Trace elements (micronutrients)	*Side effects* – Precipitation of urate, oxalate or cystine stones if given in large doses.
Zinc Oysters, shell fish, poultry, cheese, meat, nuts, whole grain, dry beans 12–15 mg 50 mg of elemental zinc/day p.o.	Acrodermatitis enteropathica is an AR disorder resulting from malabsorption of zinc Skin – Psoriasis-form lesions symmetrically distributed in periorifacial regions, sacral areas and bony prominences are the most common cutaneous manifestations. Vesiculobullous and pustular lesions, erosions and crusts may be the earliest presenting lesions. Non-scarring alopecia of the scalp is characteristic and may extend to the eyebrows, eyelids and even the whole body. White spots on the nails and paranasal erythema may be observed. Also angular stomatitis and glossitis. Growth retardation occurs in long-standing cases. Blepharitis, conjunctivitis, photophobia and nyctalopia are some of the ophthalmic manifestations. GI system – Anorexia, decreased taste. In some diarrhoea with steatorrhoea. Decreased wound healing Other features: Growth retardation and lack of secondary sexual and genital development (due to low testosterone levels). Delayed wound healing.
Magnesium Green vegetables, nuts, dried beans, whole grains, seeds, meats 700 mg/day	Behaviour changes: Irritability, emotional lability and schizoid behaviour. Muscle pain, weakness. Irritability, tremor, ataxia, carpopedal spasm. Hyperreflexia, confusion, hallucinations, epileptiform convulsions.
Phosphate All natural foods, meats, milk products, grains 800–1200 mg.	Nausea, weakness, osteoporosis
Chromium Cereal, meat 50–200 mcg	Cardiac arrhythmia Haemolysis Neuroencephalopathy Glucose intolerance
Manganese Cereals, green vegetables 2.5 mg	Transient dermatitis, discolouration and slow growth of hair, nausea, vomiting, weight loss. Increased risk of neoplasia, especially colonic cancer.
Copper 2–3 mg Copper sulphate 5 mg/day p.o.	Menke's kinky (steely) hair disease is a sex-linked abnormality caused by defect in intestinal absorption of Cu. Affected infants show progressive cerebral degeneration, retarded growth, abnormally sparse and brittle hair, arterial lesions and scurvy-like bone changes. Pili torti (twisted hair), trichorrhexis nodosa (bamboo hair) and monilethrix (beaded hair)
Selenium Cereals, eggs, onions 70 µg/day men 55 µg/day women Sodium selenite or selenomethionine up to 500 µg/day p.o. or parental	Whitening of finger nail beds, loss of pigment of hair and skin with thinning, curling of hair (pseudo-albinism). Pancreatic and hepatic necrosis seen in children suffering from kwashiorkor may be due to selenium deficiency. Peripheral neuropathy with profound muscle weakness and muscle pain. Cardiomyopathy, arrhythmias and chronic CHF can develop.

Diseases, clinical conditions and activities associated with oxidative damage to lipids, proteins and DNA are listed in Table 5.

Deficiencies in antioxidant micronutrients

Major dietary sources of micronutrients with antioxidant function are fruits, vegetables and plant oils. In general these are recognized as essential, because deficiency causes development of a defined disease. For example, early indicators of vitamin E deficiency are related to damage to cell membranes and leakage of cell contents into external fluids. Diagnostic signs include leakage of muscle enzymes such as creatine kinase and pyruvate kinase into plasma, increased levels of lipid peroxidation products in plasma and increased haemolysis. This is evidence that vitamin E is essential to humans for its antioxidant action.

6. METABOLIC SYNDROME

Metabolic syndrome Table 6 comprises the cluster of metabolic disorders. The other terms used for metabolic syndrome are insulin resistance syndrome, syndrome X, pluri metabolic syndrome.

Pathophysiology – Insulin resistance is characterized by a high plasma insulin concentration that fails to suppress plasma glucose normally. A central feature is unresponsiveness to insulin at the cellular level because of changes in receptor binding or post-receptor mechanisms. Exposure to high free fatty acid is a common mediator. Insulin sensitivity is measured by various means. A simple clinical method relates to fasting glucose to insulin concentration, using a mathematical formula known as HOMA-IR (homeostasis model assessment for insulin resistance). Insulin resistance is closely related to impaired glucose tolerance, diabetes and risk of heart disease.

Hypertension and insulin resistance. The relationship between insulin resistance and hypertension appears to be indirect because: (a) Controlling hypertension does not improve glucose tolerance or hyperinsulinaemia. (b) Patients with insulinoma are not hypertensive. Raised BP from increased insulin concentration may also result acutely from insulin-stimulated renal tubular re-absorption of sodium.

Other components of metabolic syndrome include polycystic syndrome and depression which may be partly explained by disturbances in insulin, cortisol and sex hormones, with reduced sex hormone-binding globulin.

Dyslipidemia. High LDL cholesterol and high triglycerides are features of metabolic syndrome. Elevated plasma small dense LDL (the most atherogenic subfraction of LDL) has been identified as a key feature in association with elevated triglyceride and LDL cholesterol. Individuals with these particles are at greater myocardial risk. Concentrations of small dense LDL are also increased in individuals with greater abdominal fat accumulation (large waist circumference).

Role of intra-abdominal fat – Increased abdominal fat mass (particularly the intra-abdominal fat depot) is easily recognized as an 'apple-shaped' torso and may have a direct intermediary role in the development of metabolic syndrome.

Table 5: Conditions leading to oxidative damage

ARDS (some forms)	*Ageing*
Alcoholism	Alzheimer's disease
AR, RA	Angina
AROS	Atherosclerosis
Cancer (some forms)	Cataract formation
Dermatitis (some forms)	Diabetes mellitus
Emphysema	Excessive exercise
Excess consumption of polyunsaturated fatty acids	Favism Hyperoxia
Hypertension	Infertility (some conditions)
Iron overload	Selenium deficiency
Ischemia/reperfusion injury	Malignant hyperthermia
Malaria	Parkinson's disease
Mechanical trauma to tissues	Retinopathy
Radiation injury	Smoking
Sunburn	Vitamin E deficiency
Muscular dystrophy	

Table 6: Features of metabolic syndrome

Endocrine and biochemical abnormalities
• Glucose intolerance
• Hyperinsulinaemia
• Insulin resistance
• Hypercortisolism
• Hypertriglyceridemia
• Low high-density lipoprotein
• Raised, small density low-density lipoprotein cholesterol
Overt pathophysiological conditions
• Type 2 DM
• Coronary heart disease
• Polycystic ovary syndrome
• Central fat distribution
• Morbid obesity
• Stress and depression
• Hypertension
• Non-alcoholic steatohepatitis

The liver accumulates triglycerides, such that non-alcoholic steatohepatitis is a common feature of increased intra-abdominal fat and metabolic syndrome. Increase in plasma free acid flux is a feature of central fat deposition; this may evoke and/or exacerbate the metabolic disorders: (a) Free fatty acids inhibit peripheral glucose metabolism and reduce insulin sensitivity. (b) Increased hepatic availability of free acids could stimulate hepatic free acid esterification and increase synthesis of LDL, thus increasing plasma triglyceride concentration, leading to increased small dense LDL. (c) Free fatty acids may inhibit cholesterol esterification, thereby reducing acquisition of cholesterol by HDL.

Skeletal muscle mass – A high waist: hip circumference ratio is found in individuals with a large waist (high abdominal fat accumulation), small hips (small amounts of gluteal fat or low muscle mass) or both. A relatively low hip circumference is known to be connected with many components of the metabolic syndrome. Type 2 diabetes is related more strongly to waist: hip ratio than to waist circumference alone, and low hip circumference and high waist circumference both, independently, predict type 2 diabetes.

Muscle is a major site of insulin action and glucose oxidation, and type 2 diabetes and metabolic syndrome are associated with a relative deficiency of type I (oxidative) muscle fibres.

An increase in proportion of white type II (glycolytic) muscle fibres and a decrease in red, oxidative muscle fibres is associated with metabolic complications.

Metabolic syndrome and fatal growth. There are striking relationships between markers of poor early growth (birth weight, length, weight at 1 year) and features of metabolic syndrome in later life. Two hypotheses have been used to describe these:

The 'thrifty phenotype' hypothesis for type 2 diabetes:

- Undernourishment during fatal or early life has an adverse effect on the structure and/or function of β-cells in the pancreas and peripheral tissues (primarily skeletal muscle)
- This limited glucose-insulin metabolism can cope in an undernourished environment
- In a good nutritional environment, the deficiencies in β-cell function are exposed, resulting in peripheral tissue sensitivity to insulin action, impaired glucose tolerance and diabetes.

Principles of 'programming' hypothesis:

- Undernutrition in early life has permanent effects
- Undernutrition has different effects at different times in early life
- Rapidly growing features and neonates are more vulnerable to undernutrition
- Permanent effects of undernutrition include reduced cell numbers, altered organ structure and resetting of hormonal axes.

Metabolic syndrome and inflammation C-reactive protein is a marker of inflammation. Elevated CRP correlates significantly with features of metabolic syndrome, including adiposity, hyperinsulinaemia, and insulin sensitivity index, hypertriglyceridemia, low LDL cholesterol and type 2 diabetes.

CRP is produced by and released by the liver under stimulation of cytokines including interleukin-6 (IL-6), IL-1 and tumour necrosis factor. Adipose tissue is now recognised as a major endocrine organ, and the relationship between CRP and adiposity could be explained by the findings that adipose tissue is a source of or production and release of cytokines. Plausible biochemical mechanisms link some of these components; e.g. cytokines provoke *de novo* hepatic fatty acid synthesis and interfere with the activity of lipoprotein lipase (the essential enzyme responsible for catabolism of triglyceride rich lipoprotein). In addition, cytokines can stimulate lipolysis with consequent increase in fatty acids that may in turn lead to impaired insulin sensitivity, and may impede direct insulin-stimulated glucose uptake.

Management of metabolic syndrome – (a) Lifestyle changes to reduce risks and maintain healthy weight and body fat distribution. Maintaining BMI at 21–22 kg/m^2 is advantageous for those at risk for genetic or other reasons. (b) Minimize physical inactivity. (c) Daily moderate exercise at least 30 minutes/day (d) No smoking. (e) Drugs in special situations – (i) Metformin improves glucose tolerance and lipids, and increases fertility in women with polycystic ovary syndrome. (ii) Thiazolidonones increase glucose tolerance, improve lipoprotein profile and modify fat distribution towards a less central abdominal/intra-abdominal pattern. (iii) Anti-obesity drugs such as orlistat achieve wt. loss, and more importantly, reduce weight gain in the long term, which tends to reverse or delay most features of metabolic syndrome.

7. DISORDERS OF WATER AND ELECTROLYTE METABOLISM

WATER METABOLISM

Normal Water Metabolism

Under normal conditions the body gains water from oral fluid intake, from diet, and as end-product of metabolism (about 500 mL/day). Water is normally lost through the skin (about 500 mL in temperate climates), through the lungs in the breath (about 700 mL/day), in the faeces

(about 50 mL/day) and in urine. The renal loss of water is accurately regulated to maintain the osmolality of body fluids between 280-300 mosmol/kg of water. Thus, in the anuric patient intake of about 750/mL day is required to maintain total body water constant.

Disorders of Water Balance

Since cell membranes in general are freely permeable to water, the osmolality (concentration of the solute in a solution per unit of solvent) of extracellular fluid [(ECF) 290 mosm/kg water)] is about equal to that of intracellular fluid (ICF). The term disorders of water metabolism is restricted to disturbances in osmolality, though mixed disorders or salt and water homeostasis are frequent.

Water Excess

1. Acute renal failure with oliguria or anuria. Glucocorticoid deficiency – Addison's disease, anterior pituitary failure.
2. Syndrome of inappropriate ADH secretion – Malignant tumours such as oat cell carcinoma of bronchus, head injury, acute alcoholism, encephalitis, lung disease, e.g. pneumonia or TB; myxoedema, acute porphyria.
3. Drug therapy, e.g. carbamazepine. Severe chronic renal failure and intermittent haemo-and peritoneal dialysis when intake is excessive.
4. Hypothalamic lesions.
5. Compulsive water and beer drinking.
6. Inappropriate IV fluid therapy.
7. Congestive heart failure. Liver disease.
8. Complication of transurethral resection of prostate, colorectal washes, total bowel irrigation.

Symptoms and Signs

1. Arising from CNS – Nausea, vomiting, headache, drowsiness, fits and coma.
2. Peripheral oedema – is not a feature of water excess alone.

Investigations – Diagnosis confirmed by finding a low plasma osmolality and low plasma sodium concentration in absence of manifestations of sodium depletion.

Treatment – Restriction of water intake to about 5000 mL/day. Hypertonic saline infusion if severe hyponatremia (plasma sodium <115 mmol/litre).

Water Deficiency

1. Water scarcity.
2. Inability to signify thirst – Severe illness, impaired consciousness, intubation or ventilation.
3. Severe dysphagia.
4. Cranial diabetes insipidus especially if GI losses, burns, chronic renal failure, diuretic phase of acute renal failure.
5. Nephrogenic diabetes insipidus.
6. Osmotic diuresis – diabetic ketotic coma, non-ketotic hyperosmolar diabetic coma.

Clinical features – (i) Thirst is the main symptom. (ii) In advanced cases cerebral disturbances leading to confusion, coma and even death.

Investigation – Rise in plasma osmolality and plasma sodium (to over 180 mEq/litre).

Management – Increased intake of water, if necessary IV 5% dextrose for acute hypernatremia or half normal saline (0.45/sodium chloride for chronic) hypernatremia, if unable to tolerate oral water. Over-rapid replacement should be avoided as intracerebral bleeding may occur as shrunken brain tissue is rehydrated.

DISORDERS OF SODIUM METABOLISM

Control of Sodium Balance

Under normal conditions, plasma sodium concentrations are finely maintained within narrow range of 135–145 mmol/L despite great variations in water and sodium intake. Main determination of plasma sodium concentration is the plasma water intake (thirst or habit), insensible losses such as sweat and urinary dilution. The last of these under most circumstances, the most important and is predominantly determined by arginine vasopressin, which is synthesised in the hypothalamus and then stored in and released from the posterior pituitary. In response to arginine vasopressin, concentrated urine is produced by water reabsorption across the renal collecting ducts. This is mediated by specialised cellular membrane transport proteins called aquaporins.

Sodium Excess (Hypernatremia)

Classification

See Table 7.

Clinical features – (a) Altered mental status is the most frequent manifestation, ranging from mild confusion and lethargy to deep coma. (b) Peripheral and pulmonary oedema, pleural effusions and ascites. (c) Systemic hypertension – When cardiac function is satisfactory and plasma protein concentration normal, increase in extracellular fluid volume also causes hypervolemia, which increases cardiac filling pressure and cardiac output with resultant hypertension. This occurs in primary aldosteronism and acute glomerulonephritis. (d) Oedema with signs of hypovolemia – postural hypotension, poor peripheral circula-

Table 7: Classification of hypernatremia
Hypovolaemia
Dermal losses – for example burns, sweating
Gastrointestinal losses – for example, vomiting, diarrhoea, fistulas
Postobstruction
Acute and chronic renal disease
Hyperosmolar non-ketotic coma*
Hypervolaemia
Iatrogenic (hypertonic saline, tube feedings, antibiotics containing sodium, or hypertonic dialysis)
Hyperaldosteronism †
Euvolaemia
Diabetes insipidus (central, nephrogenic, or gestational)
Hypodipsia
Fever
Hyperventilation
Mechanical ventilation
*Sodium often raised, even after correction for glucose. Typically mildly elevated sodium ~ 147 mmol/l, so rarely a clinical problem.

tion and oliguria (which is also seen in sodium depletion) occurs in hypoalbuminaemic states. (e) Hypernatremia leads to cellular shrinkage because of efflux of water leading to osmotic damage to muscles causing rhabdomyolysis, parenchymal bleed or subarachnoid/subdural bleed in brain.

Investigations – Plasma sodium is usually normal, but may be low if water is retained in excess of sodium, or raised, as in primary aldosteronism.

Treatment – The plasma Na^+ concentration should be corrected by no more than 10 mM/d, which may take longer than 48 h in patients with severe hypernatremia (>160 mM). A rare exception is patients with acute hypernatremia (<48 h) due to sodium loading, who can safely be corrected rapidly at a rate of 1 mM/h. (a) Diuretics. (b) Plasma protein infusion if hypovolemia is life-threatening. (c) Aldosterone antagonist spironolactone if hyperaldosteronism as in Conn's syndrome, cirrhosis and nephrotic syndrome. (d) Haemo- or peritoneal dialysis if inadequate response to diuretic therapy particularly if the disorder of fluid and electrolyte metabolism is complex and acidosis is also present.

Free water should be administered either orally or by nasogastric tube or through intravenous fluid, e.g. dextrose containing IV solution (D5%) with blood glucose monitoring.

Free water deficit is calculated as follows:

A. First step: Estimate Water Deficit
   1. Estimate total-body water (TBW): 50% of body weight in women and 60% in men
   2. Calculate free-water deficit $[(Na^+ - 140)/140J \times$ TBW
   3. Administer deficit over 48-72 hr, without decreasing plasma Na^+ concentration by >10 mM/24 h

B. Ongoing Water Losses
   4. Calculate free-water clearance = $V \times [1 - (U_{Na} + U_K/P_{Na})]$ where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$ and P_{Na} is plasma $[Na^+]$

C. Insensible Losses
   5. 10 mL/kg per day: less if ventilated, more if febrile

D. Total
   6 Add components to determine water deficit and ongoing water loss; correct the water deficit over 48-72 h and replace daily water loss. Avoid correction of plasma $[Na^+J$ by >10 mM/d.

Patients with central DI should respond to the administration of intravenous, intranasal or oral DDAVP. Patients with NDI due to lithium may reduce their polyuria with amiloride.

Thiazides may reduce polyuria due to NDI, ostensibly by inducing hypovolemia and increasing proximal tubular water reabsorption. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat polyuria associated with NDI.

Sodium Deficiency (Hyponatremia)

Classification

See Table 8.

Clinical features – Sunken eyes and cheeks. Weakness, faintness on standing, muscular cramps in legs and thirst. Cold hands and feet and sometimes peripheral cyanosis. Skin inelastic and low intraocular pressure. Tachycardia and weak pulse. Postural hypotension early sign, ultimately circulatory collapse and death may occur.

Hyponatremia leads to cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic ECF to the ICF. The symptoms of hyponatremia are primarily neurologic, reflecting the development of cerebral edema within a rigid skull. Acute hyponatremic encephalopathy ensues when these volume regulatory mechanisms are overwhelmed by a rapid decrease in tonicity, resulting in acute cerebral edema. Early symptoms can include nausea, headache, and vomiting. However, severe complications can rapidly evolve, including seizure activity, brainstem herniation, coma, and death. A key complication of acute hyponatremia is normocapneic or hypercapneic respiratory failure; the associated hypoxia may amplitude the neurologic injury.

Investigations – Plasma sodium concentration may be low or normal. Raised plasma urea or creatinine indicates

Table 8: Classification of hyponatremia

A. Hypovolemic hyponatremia
1. Excessive sweating.
2. GI fluid loss – prolonged vomiting, diarrhoea, fistulae, paralytic ileus.
3. Excessive renal loss – (a) Mineralocorticoid deficiency – Addison's disease, hypoaldosteronism. (b) Renal salt wasting – chronic pyelonephritis, renal calculus disease, analgesic nephropathy, after relief of urinary obstruction.
4. Burns, pancreatitis, trauma.
5. Excessive diuretic therapy.
6. Excessive ultrafiltration by haemo- or peritoneal dialysis.
B. Euvolemic hyponatremia
1. Glucocorticoid deficiency
2. Hypothyroidism
3. Stress
4. Drugs
5. SIADH
C. Hypervolemic hyponatremia
1. Congestive cardiac failure
2. Nephrotic syndrome
3. Cirrhosis
4 Acute or chronic renal failure

impaired renal function. Fluid input/output chart and daily weighing of patient and CVP line necessary.

Management – Acute hyponatremia developing within 24 hrs carries a risk of cerebral oedema, so prompt treatment is indicated with apparently small risk of central pontine myelinolysis. Patients with chronic hyponatremia are at risk for central pontine myelinolysis if plasma Na^+ concentration is corrected by >8–10 mM within the first 24 h and/or by >18 mM within the first 48 h. Alcoholics with malnutrition, elderly women on thiazide diuretics, and patients with hypokalaemia or burns are at increased risk of myelinolysis. Fluid restriction (<1 litre/day) is the initial approach to treating chronic asymptomatic hyponatremia, and Demeclocycline is drug of choice for SIADH if fluid restriction alone does not restore sodium concentrations. Aquaretics (e.g. tolvaptan, lixivaptan) induce water diuresis without affecting urinary electrolyte or solute excretion and help in correction of hyponatremia in cirrhosis, heart failure, and SIADH. Moreover restriction of fluid may not be necessary with these agents.

DISORDERS OF POTASSIUM METABOLISM

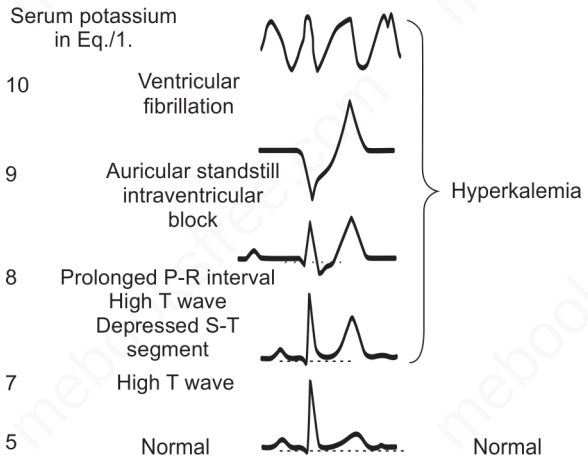
Potassium Excess (Hyperkalaemia)

1. Inadequate excretion – Renal failure, acute or severe chronic tubular disorders, adrenal insufficiency, Addison's disease, hypoaldosteronism, potassium sparing diuretics.
2. Shift of potassium from tissues – Acidosis (metabolic or respiratory). Tissue injury (muscle damage, haemolysis, internal bleeding). Hyperosmolality. Insulin deficiency. Hyperkalaemic periodic paralysis.
3. Excessive intake (especially with impaired renal function).

Clinical features – Sudden cardiac arrest may be the first manifestation. Occasionally generalised weakness of skeletal muscles.

Investigations

1. Serum K level >5.0 mEq/L.
2. ECG changes – Stages – (a) Shortening of QT interval and tall peaked T waves (serum K >5.5 mEq/L). (b) Widening of QRS complex, prolongation of PR interval, disappearance of P waves, nodal and ventricular arrhythmias (serum K >6.5 mEq/L) (c) Finally QRS complex merges with T wave in a sine wave pattern with ventricular asystole or fibrillation.



Treatment – Plasma potassium >6.0–6.5 mEq/litre is indication for immediate therapy. (a) Calcium gluconate – 5–10 mL of 10% solution may prevent sudden cardiac arrest. (b) IV glucose 300–500 mL 20% plus soluble insulin 1 IU /3 g glucose in 20 minutes. (c) Sodium bicarbonate 500 ml in 1.4% solution in 1–2 hours (only in absence of serious sodium excess). Intravenous bicarbonate has no role in the acute treatment of hyperkalemia, but may slowly attenuate hyperkalemia with sustained administration over several hours. (d) Ion-exchange resin – Calcium polystyrene sulphonate may be given orally (15 g qds.) or rectally (with 50 mL 70% sorbitol and 100 ml water) to remove potassium from the body. (e) Dialysis is rarely required. (f) Drugs and other preparations containing potassium must be stopped.

Potassium Deficiency (Hypokalaemia)

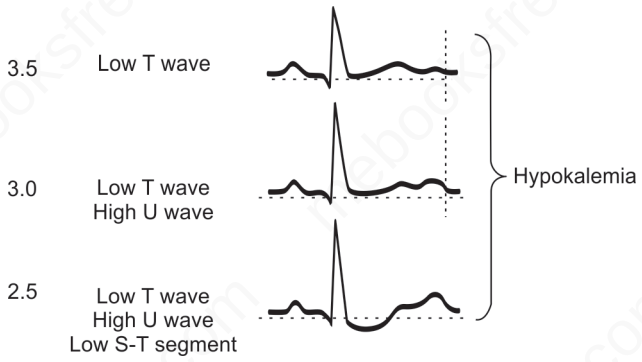
1. Gastrointestinal – Inadequate dietary intake (rarely sole cause), GI fluid loss – Prolonged vomiting, diarrhoea, fistulae, mucus secreting adenomas, ureterosigmoid anastomosis, paralytic ileus.

2. Renal loss – Diuretics (thiazide, loop, osmotic) – Metabolic alkalosis. Excess cortisol – Aldosteronism primary or secondary, Cushing's syndrome, exogenous steroids. Renal tubular disorders – Renal tubular acidosis, leukaemia, antibiotics, magnesium depletion.
3. Due to shift in the cells – Hypokalaemic periodic paralysis. Alkalosis. Insulin effect.

Clinical features – Muscular weakness, tetany and fatiguability, thirst, polyuria, paralytic ileus and cardiac arrhythmias.

Investigations – (a) Serum K <3.8 mEq/L Metabolic alkalosis often present unless hypokalaemia is due to diarrhoea or renal tubular acidosis. Mild proteinuria usual. (b) ECG changes – ST segment depression and appearance of U waves. Severe hypokalaemia may produce premature ventricular and atrial contractions, and tachyarrhythmias.

Treatment – Treatment of cause. If necessary oral potassium (20–100 mEq/day), fruit juice, coconut water, or IV (not to exceed 40 mEq/L, rate of infusion not to exceed 10 mEq/hour). Care must be taken in patients with impaired renal function to avoid hyperkalaemia. Potassium sparing diuretics, e.g. triamterene 100 mg/day or spironolactone 25 mg. qds. Hypokalaemia and hypocalcemia may co-exist and hence correct both. Hypomagnesemia also needs to be corrected.



DISORDERS OF PHOSPHATE METABOLISM

Serum phosphate levels are controlled primarily by the rate of proximal renal tubular reabsorption.

Hyperphosphatemia

Clinical features – Most often mild and asymptomatic. In acute severe hyperphosphatemia symptoms are related mainly to those of accompanying hypocalcemia – tetany, muscle cramps, paraesthesiae and seizures can occur. Chronic hyperphosphatemia is an important factor in development of secondary hyperparathyroidism in progressive kidney failure.

Table 9: Causes of hyperphosphatemia

1. ***Impaired renal phosphate excretion***
   - Renal insufficiency
   - Familial tumoural calcinosis
   - Endocrinopathies
   - Acromegaly
   - Hypoparathyroidism
   - Pseudohypoparathyroidism
   - Heparin
2. ***Increased extracellular phosphate***
   - Rapid administration of phosphate
   - Liposomal amphotericin B
   - Phosphate salts
   - Rapid cellular catabolism or lysis
   - Catabolic states
   - Tissue injury
   - Hyperthermia
   - Fulminant hepatitis
   - Crush injuries
   - Cellular lysis
   - Hemolytic anemia
   - Rhabdomyolysis
   - Tumour lysis
3. ***Transcellular shifts of phosphate***
   - Metabolic acidosis
   - Respiratory acidosis

Management (a) Volume expansion to improve GFR in acute syndrome. (b) Phosphate binding aluminium hydroxide antacids and sevalamer to limit phosphate absorption. (c) Haemodialysis is the most effective therapy, especially in tumourlysis syndrome and particularly if symptomatic hypocalcemia cannot be adequately treated for fear of inducing widespread soft-tissue calcification.

Hypophosphatemia

Clinical features: Hypophosphatemia is recognized most often in critically in patient, alcoholics or other malnourished individuals, decompensated diabetics, and those with acute infections or pulmonary disorders. In severe hypophosphatemia, common are neuromuscular symptoms ranging from progressive lethargy, muscle weakness and paraesthesiae to paralysis, coma, and even death.

Haematological – haemolysis, platelet dysfunction with bleeding and impaired leucocyte function.

Treatment For severe hypophosphatemia IV phosphate at rate of 2 to 8 mm/hr of elemental phosphorus over 4 to 8 hrs often corrects hypophosphatemia. Less acute cases can be managed with oral or enteral phosphate supplements given as total of 1 to 2 gm/day of potassium phosphate in divided doses 3–4 times a day. It is necessary to avoid a serum calcium-phosphorus product >50 to reduce the risk of heterotopic calcification.

Table 10: Causes of hypophosphatemia

1. **Reduced tubular phosphate reabsorption**
• Excess PTH of PTHrp
• PTHrP-dependent hypercalcaemia of malignancy
• Secondary hyperparathyroidism
• Vitamin D deficiency/resistance
• Calcium malabsorption / deficient intake
• Imatinib
• Rapid selective correction of severe hypomagnesemia
Excess phosphatonins
• Familial hypophosphataemic rickets
• Autosomal dominant hypophosphataemic rickets
• Tumour - induced osteomalacia syn. (TIO)
• Fibrous dysplasia
• Epidermal naevus syndrome.
• Idiopathic hypercalciuria
Intrinsic renal disease
• Fanconi syndrome(s), other renal tubular disorders
• Cystinosis
• Amyloidosis
• Hemolytic uremic syndrome
• Magnesium deficiency
• Wilson's disease
• Multiple myeloma
• Heavy metal toxicity
Rewarming or hypothermia NP2a or NPt 2c mutations
Other
• Poorly controlled diabetes, alcoholism
• Hyperaldosteronism
• Postpartial hepatectomy
• Post renal transplantation
• Drugs or toxins:
Ethanol
Acetazolamide
High dose oestrogens
High dose glucocorticoids
Calcitonin
Bisphosphonates
Paraquat
2. **Shift of extracellular phosphate into cells or bone**
Acute interstitial shifts
• IV glucose, fructose
• Insulin therapy for hyperglycemia, diabetic ketoacidosis
• Catecholamines (terbutaline, dopamine)
• Thyrotoxic periodic paralysis
• Acute respiratory alkalosis, salicylate intoxication, acute gout
Contd...

Contd...

• Gram-negative sepsis, toxic shock syn.
• Recovery from acidosis, starvation, anorexia nervosa, hepatic failure
Rapid cellular proliferation
• Leukemic blast crisis
• Intensive erythropoietin, G-CSF therapy
Accelerated net bone formation
• Post-parathyroidectomy
• Osteoblastic metastases
• Tr. of vitamin D deficiency
• Antiresorptive therapy of severe Paget's disease
3. **Impaired intestinal phosphate absorption**
• Aluminium containing antacids

Table 11: Causes of hypermagnesaemia

Causes:
1. Excessive magnesium intake – Cathartics, antacids, enemas – Intestinal obstruction or perforation following magnesium ingestion – Parenteral magnesium
2. Rapid mobilization from soft tissues – Burns – Cardiac arrest – Shock, sepsis – Trauma
3. Impaired magnesium excretion – Familial hypocalciuric hypercalcaemia – Kidney failure
4. Other – Adrenal insufficiency – Hypothermia – Hypothyroidism

DISORDERS OF MAGNESIUM METABOLISM

Magnesium like calcium, plays a critical physiological role in neuromuscular function, but also as a component of the mineral phase of bone.

Clinical features do not appear unless serum magnesium is >4 mEq/L. Hypotension may be one of the earliest signs. Lethargy, weakness, with reduction or absent tendon reflexes, can progress to stupor or coma with respiratory insufficiency at serum concentrations >8 to 10 Eq/L. Facial flushing and pupillary dilation can occur. Hypotension may be complicated by relative bradycardia, heart block and ultimately asystole.

Table 12: Causes of hypomagnesemia

Causes
1. Impaired intestinal absorption
– Malabsorption syndrome
– Hypomagnesemia with secondary hypocalcemia
2. Increased intestinal losses
– Excessive GI losses: Diarrhoea, vomiting
– Prolonged intestinal drainage
3. Defective renal tubular magnesium reabsorption
Genetic magnesium wasting syndrome
– Autosomal dominant hypocalcemia
– Familial hypomagnesemia with hypercalciuria
– Hypomagnesemia with hypertension and hypercholesterolemia
Renal disease (acquired)
– Postobstruction acute tubular necrosis (diuretic phase)
– Renal transplantation
– Tubulointerstitial disease
Drugs and toxins
– Aminoglycosides
– Digoxin
– Amphotericin B
– Diuretics
– Cyclosporine
– Ethanol
4. Rapid shifts of magnesium out of extracellular fluid
– Intracellular redistribution
– Correction of respiratory acidosis
– Recovery from diabetic ketoacidosis
– Refeeding syndrome paralysis
– Thyrotoxic periodic paralysis
5. Accelerated bone formation
– After parathyroidectomy
– Calcitonin therapy
– Osteoblastic metastases
– Treatment of vitamin D deficiency
6. Other losses
– Blood transfusions
– Extensive burns
– Pancreatitis
– Pregnancy (third trimester and lactation)
– Excessive sweating

Treatment: Identification and interruption of source of magnesium and use of cathartics or enemas to accelerate clearance from GI tract, and vigorous hydration. Haemodialysis in refractory cases with advanced kidney insufficiency. Calcium administered IV in doses of 100–200 mg over 1–2 hours, has been reported to provide temporary improvement in signs and symptoms of hypermagnesemia.

Treatment Patients with mild asymptomatic hypomagnesemia can be given oral magnesium salts 480 to 720 mg/d. Symptomatic or severe hypomagnesemia, especially if complicated by hypocalcemia (<1 mEq/L) infusions of 2 to 4 mEq/hr are needed to maintain serum magnesium in range of 2 to 3 mEq/L. In patients with active seizures or urgent indications, infusion must be preceded by slowly administered bolus of 10 to 20 mEq/hr for first hour, followed by rate of infusion 10–15 mEq/hr for first 1 to 2 hrs. only. In patients with impaired kidney function serial monitoring of serum magnesium must be done.

8. ACID-BASE DISTURBANCES

Acid-base disturbances can be easily diagnosed using a four step process. 1. Determination of serum pH. 2. Calculation of serum anion gap. 3. Estimating degree of compensation. 4. Calculation of excess anion gap.

ARTERIAL BLOOD GASES

Assessment of patient's acid-base status begins with measurement of ABG. The normal range of pH is 7.35–7.45, normal pCO_2 is 22–26 mmol/L Table 13.

Notice that the expected change occurs in the same direction in primary metabolic disorders and in the opposite direction in primary respiratory disorders. The degree of compensation for simple acid-base disorder is shown in Table 14.

Anion Gap

The negatively charged anions and the positively charged cations are equal for purposes of electrical neutrality. If so, then the unmeasured anions and unmeasured cations can be determined using the serum chloride (Cl), bicarbonate (HCO_3) and sodium (Na).

Anion gap = Plasma Na^+ – Plasma Cl^- + Plasma HCO_3

Normal Anion Gap

In some types of metabolic acidosis, reduced bicarbonate in plasma is associated with increase in plasma chloride resulting in normal anion gap.

Table 13: pH alterations in primary acid-base disturbances

Disorder	*pH*	*HCO_3^- mEq/L*	*pCO_2 mm Hg*
Normal	7.4	24	40
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓

Table 14: Degree of compensation in acid-base disturbances

Disorder	*Degree of compensation*
Metabolic acidosis	$PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$
Metabolic alkalosis	$PaCO_2$ will increase 6 mm Hg for each 10 mEq/L increase in HCO_3^-.
Respiratory acidosis	HCO_3^- will increase 1 mEq/L per 10 mm
Acute	Hg increase in $PaCO_2$
Chronic	HCO_3^- will increase 4 mEq/L per
	10 mm Hg increase in $PaCO_2$
Respiratory alkalosis	HCO_3^- will decrease 2 mEq/L per 10 mm
Acute	Hg increase in $PaCO_2$
Chronic	HCO_3^- will decrease 4 mEq/L per
	10 mm Hg increase in $PaCO_2$

Table 15: Causes of abnormal serum anion gap

Increased anion gap
Common
• Methanol intoxication
• Uraemia
• Diabetic ketoacidosis
• Ethanol
• Drugs: Isoniazid, salicylates
• Lactic acidosis A and B
• Rhabdomyolysis
Uncommon
• Hyperalbuminaemia
• Administered anions
Decreased anion gap
• Hypoalbuminaemia
• Paraproteinemia (multiple myeloma)
• Spurious hypercholeraemia (Bromide intoxication)
• Spurious hyponatremia
• Hypermagnesaemia

Table 16: Metabolic acid-base disturbances

Metabolic acidosis:
A. With high anion gap –
1. Ketoacidosis – diabetic, starvation, alcoholic.
2. Lactic acidosis – Type A – shock (including cardiac arrest, hypoxia). Type B – biguanide, fructose, sorbitol, ethanol, methanol, severe liver disease.
3. Other conditions – Uraemia, salicylate poisoning.
B. With normal anion gap –
1. GI bicarbonate loss – diarrhoea, intestinal, pancreatic and biliary fistulae, ureterosigmoid-ostomy, ileostomy, colostomy.
2. Renal tubular acidosis.
3. Ingestion of e.g. acetazolamide, ammonium chloride, certain amino acids.
4. Rapid IV hydration (dilutional acidosis).

The normal anion gap is 12–15 mEq/1. An increase of over 15 mEq/1 is considered to be abnormal (*see* Table 15).

In primary acid-base disorders and in a case of simple metabolic acidosis the anion gap will increase by one mEq/L for every 1mEq/L decrease in serum bicarbonate (one for one ratio). However, this relationship is altered in mixed acid-base disorders due to partial compensatory mechanism by the kidneys and lungs to maintain homeostasis. A comparison in the 'increment' change in anion gap relative to change in bicarbonate concentration can aid in identifying acid-base disorders. This concept is used in calculation of excess anion gap and diagnose mixed acid-base disorders. Decrease in serum bicarbonate concentration = increase in serum anion gap (see Table 16).

Clinical Features

Metabolic acidosis produces immediate hyperventilation. In severe acidosis cardiac output falls and state of shock results. Other effects include cardiac arrhythmias, dilatation of vessels (particularly cerebral) and increased risk of pulmonary oedema during fluid therapy. Hepatic removal of lactase by gluconeogenesis is depressed by severe acidosis, and this may exacerbate lactic acidosis.

METABOLIC ALKALOSIS

1. **Excessive ingestion or infusion of alkali** – Milk alkali syndrome, alkali ingestion in presence of kidney failure, forced alkaline diuresis, excessive bicarbonate therapy for metabolic acidosis.

2. **Inappropriate loss of chloride** – Vomiting or gastric drainage, diuretic therapy.
3. **Associated with hyperadrenocortisolism** – Cushing's syndrome, primary aldosteronism, Bartter's syndrome (hyperreninaemia).
4. **Severe potassium depletion**

Clinical Features

Acute alkalosis causes tetany. Apathy, confusion, drowsiness in severe long-standing alkalosis may be associated with reduced kidney function and uraemia. Compensation by hyperventilation is poor or even absent.

RESPIRATORY ACID-BASE DISTURBANCES

Respiratory Acidosis

1. *Lung disorders* – Chronic obstructive airways disease, large airway obstruction, severe asthma (uncommon).
2. *Neuromuscular and skeletal abnormalities* – Acute inflammatory demyelinating polyradiculoneuropathy, polio, myasthenia, motor neuron disease, severe obesity, kyphoscoliosis, etc.
3. *Respiratory centre disorders* – Drugs, e.g. opiates, barbiturates, benzodiazepines; organic disease affecting respiratory control.

Clinical Features

Symptom complex is labelled CO_2 narcosis. Symptoms vary from headache, blurred vision, anxiety, tremors and asterixis, to somnolence and delirium. Acidaemia induced increase in cerebral blood flow leads to increased CSF pressure and papilloedema. If systemic pH falls below 7.1, cardiac arrhythmias and hypotension can result due to peripheral vasodilatation.

Respiratory Alkalosis

1. Hyperventilation (psychogenic)
2. Excessive assisted ventilation
3. Pneumonia
4. Pulmonary embolism
5. Meningitis
6. Encephalitis
7. Hepatic failure
8. Salicylate poisoning
9. Septicaemia

Clinical features

Symptoms occur more commonly in acute resp. alkalosis and include feeling of light headedness, sacral and perioral paraesthesia, cramps, carpopedal spasm, syncope and altered sensorium. Tachypnoea accompanies hypocapnia. Supraventricular and ventricular dysrhythmias may be seen. Hypotension can result from peripheral vasodilatation.

Note: The distinction between respiratory. acidosis and metabolic alkalosis can be made by knowing the cause of the disturbance and the fact that H^+ is raised in respiratory acidosis and reduced in metabolic alkalosis.

Respiratory alkalosis occurs early in septicaemia which should be suspected when there is no obvious cause for hyperventilation.

Diagnosis – By evaluating values of pH and $PaCO_2$, using a suitable acid base diagram. In addition the source of metabolic acidosis can often be determined calculating the plasma 'anion gap'.

Management

1. *Treatment of primary condition.*
2. *Treatment of respiratory acidosis* – (See management of respiratory failure).
3. *Metabolic acidosis* – Sodium bicarbonate – Treatment of metabolic acidosis with alkali should be reserved for severe academia (pH <7.10). Slow infusion of isotonic bicarbonate (about 800 mL/hour) and the effect assessed by re-estimation of pH and $PaCO_2$ before deciding further therapy. In cases where severe acidosis and hypokalaemia coexist, if acidosis is treated without prior or simultaneous administration of potassium salts, the hypokalaemia may be exacerbated and cardiac arrhythmias or arrest may result. Chronic therapy with alkalis may be required in some conditions associated with metabolic acidosis.
4. *Metabolic and respiratory alkalosis* – Seldom require attempts at acidification. Most metabolic alkalosis is due to potassium and chloride deficiency and adequate replacement of these is effective. However, if tetany occurs or effects on cerebral circulation suspected, breathing into a bag, oral ammonium chloride or IV arginine hydrochloride infusion is required. Indomethacin for Bartter's syndrome.

An important dictum to distinguish between simple and mixed acid-base disorder is: In contrast to simple disorders, an abnormal value of $PaCO_2$ and bicarbonate in the face of near-normal values of pH should always raise the suspicion of mixed acid-base disorder.

Table 17: Four steps to solve acid-base disorders

Step 1	Determine pH status • Acidic pH <7.35 • Alkalaemia pH >7.45
Step 2	Calculate the anion gap If > 20 mmol/L, there is primary metabolic acidosis regardless of bicarbonate level
Step 3	What is the degree of compensation? (refer Table 15)
Step 4	What is the anion gap?
	• Calculate the excess anion gap (total anion gap – normal anion gap [12 mmol/L]) and add this value to the measured bicarbonate concentration. If the calculated HCO_3 >30 mmol/L there is associated metabolic alkalosis. • It the calculated HCO_3 <23mmol/L there is associated anion gap acidosis. • In primary acid-base disorders, change in anion gap = change in bicarbonate level.

9. LYMPHADENOPATHY

Differential Diagnosis

I. **Inflammatory or Infective group** –

1. ***Acute and subacute lymphadenitis*** – (i) Local or generalized enlargement. (ii) Infected focus in neighbourhood of affected glands. (iii) Local heat. (iv) Tenderness. (v) Fever.
2. ***Tuberculosis*** – (i) Children or young adults. (ii) Adenopathy local cervical or general including mediastinal and retroperitoneal. Axillary and inguinal are usually non-specific, however when the nodes suddenly increase in size, become painful and are associated with constitutional symptoms, in absence of a known factor, tuberculosis must be suspected. (iii) Glands matted together and often caseous; may be tender. (iv) Fever always present. (v) No splenomegaly. (vi) Often tuberculosis elsewhere.
3. ***Infectious mononucleosis*** – (i) Children or young adults. (ii) Adenitis mostly cervical, may be generalized. (iii) Glands discrete, moderately enlarged, slightly tender. (iv) Moderate fever. (v) Splenomegaly. (vi) Acute onset, chills and sore throat. (vii) Leucocytosis with predominant small lymphocytes. (viii) Positive Paul-Bunnel test. (ix) Recovery in a few weeks.
4. ***Syphilis*** – (i) Usually young adults. (ii) Posterior cervical and epitrochlear glands always enlarged. Enlargement slight. (iii) Hard, painless, discrete. (iv) Fever variable. (v) Splenomegaly sometimes. (vi) Skin rash, mucous patches, joint pains, or other evidence of secondary syphilis. (vii) Positive VDRL, TPHA tests. (viii) Spontaneous recovery common.
5. ***Chancroid*** – Painful genital ulceration. Painful and tender regional lymph glands on one or both sides. Diagnosis by demonstration of H. ducreyi by direct smear or culture.
6. ***Lymphogranuloma venereum*** – (a) Primary lesion – Papule, shallow ulcer/erosion which heals rapidly. (b) Inguinal syndrome – Unilateral lymphadenopathy of femoral and inguinal glands, single or multiple and firm to start with, but soon soften to become multilocular abscesses. 'Sign of the groove'. Diagnosis confirmed by isolation of LGV agents from material aspirated from bubo. Also positive complement fixation and immunofluorescence tests.
7. ***Filariasis*** – Filarial lymphangitis and lymphadenitis affecting inguinal and axillary nodes. Fever with headache and malaise.
8. ***Systemic lupus erythematous*** – (i) Acute onset. (ii) Generalized lymphadenopathy. (iii) Recurrent septic type of fever. (iv) Flushed or erysipelas-like appearance of face. (v) Erythematous lesions on trunk and extremities, ulcers and erosions of mouth. (vi) Splenomegaly. (vii) Arthritic pain. (viii) Cardiac manifestations. (ix) Purpura. (x) ANA and Anti-ds-DNA, ENA antibodies in serum.
9. ***HIV infection*** –
   a. *Acute disease* – A glandular fever-like syndrome occurring in some before seroconversion. Sudden onset of fever, sweats, myalgia, arthralgia, headache, sore throat and diarrhoea. Generalized lymphadenopathy and sometimes transient erythematous macular rash on trunk. Spontaneous resolution of symptoms and lymphadenopathy usually in 3–14 days. Lymphopenia and thrombocytopenia and atypical lymphocytes.
   b. *Persistent generalized lymphadenopathy* – may be symptomless and resolve in course of time, or may be associated with malaise, fatigue, weight loss, anorexia, fever, night sweats and diarrhoea and may progress to AIDS. Lymph node biopsy shows marked follicular hyperplasia.

10. ***Leishmaniasis*** – Rarely the disease may be localized in the lymph nodes. History of the patient having been in area of endemic leishmaniasis. Presence of L.D. bodies can be demonstrated in the gland.
11. ***Acute viral hepatitis*** – Lymphadenopathy in some patients, with jaundice, hepatic tenderness and hepatomegaly.
12. ***Rubella*** – Suboccipital, postauricular and posterior cervical lymphadenopathy and typical rash.
13. ***Fungal infections*** – (a) *Coccidioidomycosis* – Lymphadenopathy, and infection of skin, bones, joints, spleen, liver, kidneys, meninges and brain. (b) *Histoplasmosis* – Progressive disseminated form follows haematogenous spread from lungs and is characterised by hepatomegaly, lymphadenopathy, splenomegaly, and less frequently oral or GI ulceration.
14. ***Serum sickness*** – Fever, cutaneous eruptions, arthralgia, lymphadenopathy, and albuminuria.
15. ***Tularemia*** – Local lesion, may be an infected wound or papule. After an incubation period of 1–10 days, chills and headache are followed by fever, bodyache, and enlargement of regional lymph nodes, which may proceed to a chronic indolent abscess.

II. **Reticuloses (malignant lymphomas and blood diseases):**

a. ***Acute lymphocytic leukaemia*** – (i) Children or young adults. (ii) Glands discrete, not tender. (iii) Fever moderate or high. (iv) Moderate splenomegaly. (v) Haemorrhages, stomatitis and bone pains. (vi) Diagnostic blood picture. (vii) Short course.

b. ***Chronic lymphocytic leukaemia*** – (i) Middle or old age. (ii) Glands large but discrete. (iii) Moderate splenomegaly. (iv) Irregular fever. (v) Haemorrhages. (vi) Skin eruptions.

c. ***Hodgkin's disease*** – (i) Any age. (ii) Mostly cervical, may be axillary, inguinal, abdominal or mediastinal. (iii) Glands painless and discrete. Size varying from pea to a large orange. Rubbery feel. Characteristic appearance in advanced cases is a pyramidal swelling with its base at clavicle and apex at angle of jaw. (iv) Fever. (v) Pressure symptoms common. (vi) Generalized pruritus. (vii) Splenomegaly common.

d. ***Non-Hodgkin's lymphomas*** –

a. *Low grade* – (i) Age over 50. (ii) Painless adenopathy in cervical, axillary and inguinofemoral regions. In some large abdominal masses of retroperitoneal or mesenteric lymph nodes may be the presenting feature. (iii) Spleen often enlarged at onset of disease, subsequently marked enlargement producing local symptoms and hypersplenism. Favourable prognosis. (b) *High grade* – Presents with extensive, rapidly progressing, nodal disease often with bone marrow and other extranodal involvement. Rarely disease may be confined to one nodal or extranodal site. Extralymphatic involvement is not uncommon; GI tract, thyroid, testes and bone being the more common sites.

e. ***Follicular lymphomas*** – Usually middle age. Occur in two phases. First phase relatively benign with enlargement of one or more of superficial lymph nodes, with or without splenomegaly. No constitutional symptoms. Lymph nodes moderately enlarged, discrete, firm and non-tender. This phase is followed after varying period by malignant phase characterised by development of histological features of lymphosarcoma or reticulum cell sarcoma or less commonly Hodgkin's disease.

f. ***Sarcoidosis*** – (i) Children or young adults. (ii) Generalised lymphadenopathy. Frequent involvement of pre-and post-auricular, submaxillary, epitrochlear, and para-tracheal glands. (iii) Splenomegaly (iv) Sarcoid lesions of skin, and uveitis or parotitis. (v) X-ray of chest – Bilateral involvement of hilar nodes or miliary nodular bilateral involvement or soft infiltration or dense hilar radiation. (vi) Tuberculin test – sensitivity diminished. (vii) Liver biopsy characteristic changes of sarcoidosis in majority.

g. ***Toxoplasmosis*** – Lymphadenopathy is the most common presenting feature. Painless enlargement especially of cervical lymph nodes. Nodes may be mobile, discrete and occasionally tender. Spleen seldom palpable. In some, other organs such as brain, meninges, heart, lung, liver or skeletal muscles are involved. *Diagnosis* – Dye test in which be methylene blue is used to stain live *Toxoplasma*. Also ELISA test to detect significant levels of toxoplasma-specific IgM antibody.

III. **Neoplasms** – (a) *Secondary carcinoma* – (i) Middle or old age. (ii) Glands hard, fixed and localised to a limited region; painless and not tender. (iii) Presence of a primary lesion. (b) *Sarcomas* – Synovial sarcoma, Kaposi's sarcoma.

IV. **Drugs** – Carbamazepine, allopurinol, cephaloridine, iron dextran, meprobamate, PAS, phenylbutazone, primidone, sulphadimidine and troxidone. Phenytoin may cause not only lymphadenopathy but also hepatosplenomegaly.

V. **Lipid storage diseases** – Gaucher's and Niemann-Pick disease.

VI. **Miscellaneous diseases and diseases of unknown ethology** –

a. *Mucocutaneous lymph node (Kawasaki) syndrome* Occurs in infants and children below 5, consisting of characteristic exanthem, enanthem, fever, lymphadenopathy, bilateral conjunctival injection, polyarteritis of variable severity.

b. *Sinus histiocytosis* – Generalised glandular enlargement with massive cervical lymphadenopathy, fever and leucocytosis.

c. *Amyloidosis* – Lymphadenopathy can occur with systemic amyloidosis. Evidence of other organ dysfunction.

d. *Dermatopathic lymphadenitis* – Enlarged superficial lymph nodes in exfoliative dermatitis.

e. *Lymphomatoid granulomatosis*–Lymphadenopathy more affecting intrathoracic nodes, less peripheral. May progress to frank lymphoma.

f. *Angio-immunoblastic lymphadenopathy* – Spectrum of diseases characterised by lymphadenopathy, hepatosplenomegaly, fever, autoimmune hemolytic anemia and hypergammaglobulinaemia.

g. *Multifocal Langerhans' cell (eosinophilic) granulomatosis* – Usually in childhood. Focal or generalised lymph node enlargement, and development of multiple bony lesions. Diabetes insipidus, hepatomegaly and splenomegaly may be associated.

h. *Histiocytic necrotizing lymphadenitis* (Kikuchi's disease) is usually a self-limiting illness, characterized by pyrexia, neutropenia and cervical lymphadenopathy in young women of Asian descent.

i. *Sinus histiocytosis with massive lymphadenopathy (SHML)* is a rare entity characterised by massive, painless cervical lymph node enlargement. Extranodal involvement occurs in a number of cases and affects the skin, paranasal sinuses, soft tissue and bone, etc.

Investigation of a case of lymph node enlargement

History

1. *Age* – Tuberculous lymphadenitis in childhood, secondary carcinoma in old age.
2. *Occupation* – Tularemia in hunters and butchers; sporotrichosis in farmers and gardeners.
3. *Duration* – (a) Acute swelling of a few days duration mostly pyogenic. (b) Subacute lymphadenitis of 3–4 weeks' duration may be due to streptococcal infection, tuberculosis, secondary syphilis, infectious mononucleosis or tularemia. (c) Chronic lymphadenopathies include tuberculosis, lymphomas, leukaemia, primary lymphatic tumours and secondary carcinoma. History of previous radiation treatment or operative removal.

Physical examination

Local

1. *Number of glands* – Single gland may appear to be affected for some time in tuberculosis, Hodgkin's and secondary carcinoma. Multiple in tuberculosis, Hodgkin's disease, leukaemia.
2. *Site* – (a) Neck usual site for tuberculous lymphadenitis, lymphosarcoma, and most other lymphadenopathies. (b) Inguinal gland enlargements may be due to syphilis, lymphogranuloma inguinale or chancroid. (c) The infraclavicular glands are seldom so enlarged as to be palpable except in secondary cancer or Hodgkin's disease. (d) Supratrochlear (epitrochlear) lymphadenopathy in non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, infectious mononucleosis, secondary syphilis, sarcoidosis, i.v. drug abuse. (e) Hilar and superior mediastinal lymphadenopathy in tuberculosis, histoplasmosis, sarcoidosis, pneumoconiosis, malignancy and cryptococcosis.
3. *Character* – Discrete in Hodgkin's disease and leukaemia, primary tumours of lymphatic tissue and so called "lymphadenoid" form of tuberculous lymphadenitis. Movable, discrete and painless in sarcoidosis. Matted together in tuberculosis and lymphogranuloma.
4. *Cold abscess* – in tuberculosis, lymphogranuloma, tularemia and sporotrichosis. Tuberculous glands may break through to give a typically indolent ulcer with undermined edges.

5. *Primary cause* – in the area drained by the enlarged glands; e.g. scalp if occipital or posterior auricular glands, fauces and pharynx if upper anterior cervical group, etc. Healed scar at portal of entry, scar of operative removal, or of radiation treatment.

Systemic

a. *Skin* – (i) Cutaneous tumours mostly on the face, usually in chronic lymphatic leukaemia. Sometimes generalised erythroderma, polymorphic rashes and purpura. (ii) Rash of secondary syphilis. (iii) Painless papules without surrounding erythema may be found on face, arms and legs in sarcoidosis. (iv) Eruption of lupus erythematosus.
b. *Lungs* – Pulmonary or mediastinal tuberculosis, lesions of sarcoidosis or metastatic or primary deposits in carcinoma.
c. *Abdomen* – Abdominal glands may be palpable in tuberculosis. Enlargement of spleen and liver in leukaemia and Hodgkin's disease.
d. *Genitalia* – Scar of primary sore of syphilis, or "chancre" in lymphogranuloma.
e. *Icterus* – Jaundice with lymphadenopathy may be met with in viral hepatitis (cervical glands), lymphoma, acute lymphocytic leukaemia, disseminated TB.
f. *Temperature* – raised in Hodgkin's disease, infectious mononucleosis and tularemia.

Investigations

1. *Blood picture* – for diagnosis of leukaemia, and infectious mononucleosis. Positive ANA and reduced complement C_4 levels in SLE.
2. *Special tests* – Serologic tests for syphilis. Paul-Bunnell or monospot test for infectious mononucleosis. Agglutination reaction and animal inoculation in tularemia. Autoantibodies in SLE. Liver biopsy useful in sarcoidosis and infectious mononucleosis. Serological tests for HIV infection.
3. *Radiography* – of lungs and gastrointestinal tract. Skeletal changes in sarcoidosis and sporotrichosis (multiple small areas of decalcification).
4. *Biopsy* – Needle aspiration biopsy is useful for initial evaluation of superficial lymphadenopathy. It is however not helpful in diagnosis of lymphomas and other hematologic malignancies. Lymph node biopsy tissue should be processed for culture of appropriate organisms, frozen in liquid nitrogen for lymphocyte typing or special studies for malignant cell types, and for routine histological studies.
5. *CT scan* – of abdomen in lymphoma.
6. *Lymphangiography* – of value in diagnosing site, extent, and, in certain cases, even the nature of primary lymph node enlargement.
7. *Laparotomy and laparoscopy* – Lymphomas.

10. HYPERLIPOPROTEINAEMIAS

Hyperlipoproteinaemias are disturbances of lipid transport resulting from abnormalities in synthesis or degradation of plasma lipoproteins. *Hyperlipidemia* is a rise in plasma cholesterol, triglycerides or both. Elevated cholesterol primarily refers to high low-density lipoprotein cholesterol (LDL-C) since approximately 70% of cholesterol is carried in the LDL particle.

Lipid metabolism has two pathways—1. Exogenous pathway which starts from intestinal absorption of dietary fat and cholesterol. 2. Endogenous pathway that starts with VLDL production from the liver. The former is domination in the well fed state, the latter in the fasted stage. 3. Reverse cholesterol transport is the process of removal of cholesterol from tissues and returning it to the liver. HDL (synthesised and catabolised in liver and intestine) is the main lipoprotein concerned with this process.

Table 18: Causes of hypertriglyceridemia

A. *Primary*
– Chylomicronaemia
– Familial lipoprotein deficiency
– Familial apoprotein C-II deficiency
– Elevation of VLDL
– Familial combined hyperlipidemia
– Dysbetalipoproteinaemia
– Hepatic lipase deficiency
B. *Secondary*
– Hypothyrodism
– Diabetes mellitus
C. *Associated diseases*
– Liver disease
– Obesity
– Lipodystrophy
– Glycogen storage disease

Types of lipoproteins

1. *Chylomicrons,* which transport exogenous or dietary fat.
2. *Very low density lipoproteins* (VLDL) which transport endogenous triglyceride.
3. *Low density lipoprotein* (LDL) which transport cholesterol to peripheral cells.
4. *High density lipoprotein* (HDL) which transport cholesterol from peripheral cells.

Chylomicrons and VLDL are triglyceride- rich LDL, while HDL are cholesterol-rich. The plasma lipid values permit accurate assessment of which lipoprotein is raised. Determination of plasma cholesterol and triglyceride concentration after a 12–24 hours overnight fast is usually sufficient for clinical purposes.

Classification of lipid profiles: Plasma samples in these dyslipidemias are given in Table 19.

Risk of atherosclerosis with IIa, IIb, III. For simplification type I-V approach can be replaced with three broad patterns of excess:

1. Predominantly hypercholesterolemia
2. Predominantly triglyceridaemia
3. Mixed hyperlipidemia

Other lipids

Lipoprotein [LP (a)] is an atherogenic lipoprotein particle in human plasma related in structure to LDL. In addition to CHD, LP (a) has been shown to be an independent risk factor for cerebrovascular atherosclerosis. Elevated plasma concentrations are associated with an increased risk of premature CHD. A plasma level of more than 30 mg/dL appears to confer significantly higher risk of atherosclerotic disease. Small dense LDL particles containing cholesterol ester considered to be more atherogenic than LDL particles.

(See Table 20 for causes of hyperlipidence)

Clinical presentation – of hyperlipidemia

1. *Asymptomatic* and undetected until a complication occurs such as myocardial infarction due to early atherosclerosis, or during screening of suspects such as family members.
2. (i) Xanthelasmas. (ii) Lipemia retinalis. (iii) Achilles tendon xanthomata. (iv) Palmar xanthomatas. (v) Tuberous or tuboeruptive xanthomatas. Cutaneous xanthomas are clinically subdivided into xanthelasma palpebrum, tuberous xanthomas, tendinous xanthoma, eruptive xanthoma and plain xanthomas. The presence of tendon xanthomas along with xanthelasma indicates familial hypercholesterolaemia.

Management of hyperlipidemia.

Indications – 1. Young primary hypercholesterolaemia hypertriglyceridaemic patients, especially if there is family history of early onset cardiovascular disease. 2. All hypertriglyceridaemic patients with levels in excess of 1000 mg/dL to prevent pancreatitis.

1. ***Diet*** – Calorie restriction and exercise in overweight patient. Reduction of saturated fats and replacement with unsaturated fats (vegetable) oils. Increase in carbohydrate content to about 55% of total calories.
2. ***Weight reduction*** – if overweight.
3. ***Exercise*** – helpful in lowering triglyceride and cholesterol levels.
4. ***Discontinuation of drugs*** – such as thiazide diuretics and beta-blockers can lead to reduction of cholesterol and LDL levels.
5. ***Drugs***

See Table 21 for drugs for the treatment of dyslipidemia.

Table 19: Classification of lipid profile

Type I	Chylomicronaemia alone. Serum with creamy top, clear underneath. Very rare.
Type II	Raised cholesterol as excess LDL alone (IIa) or plus some VLDL with cloudy serum (IIa). Pattern type IIb overlaps with type IV. All three are common.
Type III	Excess of chylomicron remnants in the uncommon familial dysbetalipoproteinaemia. Usually turbid.
Type IV	Mainly triglyceridaemia with VDL, VLDL excess. Cloudy with faint creamy layer.
Type V	Everything in excess including chylomicrons. Very cloudy with creamy top on standing in fridge.
	Uncommon.

Table 20: Causes of hyperlipidemia

1. Primary (genetic).
2. Secondary
– Diet rich in saturated fat
– Sedentary lifestyle
– Alcoholism
– Diabetes mellitus
– Hypothyroidism
– Nephrotic syndrome
– Cushing's syndrome
– Liver disease (obstructive)
– Drugs (steroids, thiazide diuretics, oestrogens)

Note: Ezetimibe is combined with statins in patients who are unable to take large dosages of statins or require further reduction in LDL despite maximum statin dosage. Combination of lipid-lowering therapy and calcium channel blockers (CCBs) is effective. Serum markers of atherosclerosis and vascular integrity improve most in combination group. Synergistic effects of atorvastatin and amlodipine on acute nitric oxide release/endothelial function and additive effects of the combination in improvement of arterial compliance in hypertensive hyperlipidaemic patients has been demonstrated.

6. ***Plasmapheresis, partial ileal bypass, liver transplantation*** – have been used for homozygous form of familial hypercholesterolemia since these patients respond poorly to drugs. Plasmapheresis has also been used for severe heterozygous FH.

11. INBORN ERRORS OF METABOLISM

A group of inherited disorders involving genetically determined abnormalities in wide variety of metabolic pathways or structural proteins. Each defect leads to a special clinical picture which can usually be predicted by the nature of the biochemical defect.

THE PORPHYRIAS

Porphyrias are metabolic diseases caused by defects in normal haem and porphyrin biosynthesis. The porphyrias are classified into acute (inducible) and non-acute (cutaneous) presentations. They are all transmitted in an autosomal dominant manner, except for the rare congenital porphyria, which is recessive, and porphyria cutanea tarda, which may be acquired.

Table 21: Drugs for the treatment of dyslipidemia

Drug	*Dose*	*Clinical use*	*Effects*	*Side effects*
Nicotinic acid (*Niacin)* Bile acid sequestrants	1g t.d.s.	IIa, IIb, III, IV, V	HDL↑ LDL↓	Flushing, nausea, pruritus, dizziness, hypotension, liver disease, peptic ulcer.
Cholestyramine Colestipol	8 g t.d.s.	IIa, IIb	LDL↓ HDL↑ Trigl↓	Constipation, flatulence, heartburn, nausea.
HMG-CoA reductase inhibitors				
Lovastatin Pravastatin Simvastatin Fluvastatin Atorvastatin	20–40 mg b.d 20 mg o.d. 5–40 mg o.d. 20–40 mg o.d. 10 mg b.d.	IIa, III, IV, V	LDL↓ HDL↑ Trigl↓ Apo B↓	Skin rash, myositis, elevated LFTs. Constipation, flatulence, abd. pain.
Fibrants				
Gemfibrozil Fenofibrate Benzofibrate	600 mg b.d. 200 mg o.d. 400 mg b.d.	IIb, III, IV, V	HDL↑ Trigl↓ LDL↓	Bloating, diarrhoea, headache, rash, increased risk of gallstones. Rarely myositis.
LDL oxidation inhibitor				
Probucol (Can be combined with bile resins)	500 mg b.d.	IIa, IIb	HDL↑ LDL↓	Diarrhoea, flatulence, nausea, prolonged QT interval.
Cholesterol absorption inhibitor				
Ezetimibe	10 mg o.d.	IIa, IIb	HDL↑ LDL↓	Diarrhoea. Liver enzyme elevation
Omega-3 fatty acids				
Eicosapentaenoic acid (EPA)	180 mg		Cholesterol↓	Occasional nausea and belching.
Docosahexaenoic acid (DHA) per capsule	120 mg 2 capsules t.d.s		Triglycerides↓ VDL↓ HDL↑	
MTP inhibitor Lomitapide	5 mg daily	IIa	↓VLDL	Nausea, diarrhoea, increased hepatic fat
ApoB inhibitor Mipomersen	200 mg sc weekly	IIa	↓VLDL	Injection site reaction

Molecular biology – cDNA clones have been obtained for all the enzymes of haem biosynthesis. The most striking feature in all porphyrias is the heterogeneity of the genetic lesion, except when the 'founder effect' is present (i.e. a genetic defect in an early generation is carried to later generations).

The porphyrias are classified as either hepatic or erythropoietic depending on the primary site of overproduction and accumulation of their respective porphyrin precursors or porphyrins (Tables 22 and 23).

Acute porphyrias – All patients have similar abdominal and neuropsychiatric or neurovisceral disturbances. Those with hereditary coproporphyria and variegate porphyria may also present with photosensitivity. During an attack, patients excrete massive excess of porphyrin precursors, 5-aminolaevulinic acid (ALA) and porphobilinogen (PBG) in their urine. However some patients remain asymptomatic, and may have normal excretion of porphyrin and precursors. Urine when first passed, is clear and darkens on exposure to light as porphyrinogens are converted to porphyrins. Attacks which may vary from several days to months, are commonly followed by complete remission.

Precipitating factors – Drug ingestion (barbiturates, sulphonamides, oral contraceptives), anticonvulsants such as carbamazepine, phenytoin, primidone, alcohol ingestion, endogenous or exogenous hormonal factors and infection.

I. **Acute intermittent porphyria (AIP)** – Most severe of acute porphyrias. Occurs usually in young adults.

Clinical features – *GI symptoms* – most common. Colicky abdominal pain, vomiting, severe constipation. *Motor neuropathy* may be the presenting feature. Weakness involves more limb and girdle muscles. Paraesthesiae and sensory loss impairment may occur. Epileptic fits may occur. *CVS* – Sinus tachycardia, hypertension which usually reverts to normal after acute attack. *Psychiatric* – Depression, hysteria, psychosis. Precipitating factors – Drugs especially barbiturates, pregnancy, infection, starvation.

1. ***Porphyria variegata*** – Combination of clinical features of acute intermittent and cutaneous hepatic porphyria.
2. ***Hereditary coproporphyria*** – Both systemic and cutaneous signs. Abdominal pain, vomiting and constipation are the usual presenting features.
3. ***Plumboporphyria*** – Here 5-amino-levulinic acid dehydratase activity is depressed (this also occurs in lead poisoning). Clinical picture resembles acute intermittent porphyria.

Management

1. *Reduction of porphyrin synthesis* – (a) Oral carbohydrate intake of 1500–2000 kcal/24h should be maintained throughout the attack by nasogastric tube if necessary to reduce porphyrin synthesis. If not tolerated laevulose or glucose 2 litres/day of 20% solution IV. (b) IV haematin (haem arginate) 2–4 mg/kg over 30 minutes.
2. *For skin photosensitivity* – Barrier creams and beta-carotene 90 mg daily in VP and HC. Pregnancy should be avoided if disease is active.

II. **Non- acute (cutaneous) porphyrias** – Here photosensitizing porphyrins are deposited in the upper dermis layer, these are responsible for the characteristic skin lesions.

1. ***Cutaneous hepatic porphyria*** – may be inherited or acquired. Characteristic feature is bullous dermatosis on light-exposed areas, which often causes troublesome pruritus. Hyperpigmentation is common. Biochemical evidence of liver disease. Alcohol is the most important precipitating agent.

   Management – (a) Venesection of 500 ml every 2 weeks until clinical remission or fall of haemoglobin

Table 22: Classification of porphyrias

A. Hepatic Porphyrias
1. 5-ALA dehydratase deficient porphyria (ADP)
2. Acute intermittent porphyria (AIP)
3. Porphyria cutanea tarda (PCT)
4. Hereditary coproporphyria (HCP)
5. Variegate porphyria (VP)
B. Erythropoietic Porphyrias
1. Congenital erythropoietic porphyria (CEP)
2. Erythropoietic protoporphyria (EPP)
3. X-linked protoporphyria (XLP)

Table 23: Manifestation of porphyria

1. Neurovisceral – seen in
– 5-ALA dehydratase deficient porphyria (ADP)
– Acute intermittent porphyria (AIP)
– Hereditary coproporphyria (HCP)
– Variegate porphyria (VP)
2. Blistering skin lesions
– Hereditary coproporphyria
– Porphyria cutanea tarda
– Variegate porphyria
– Congenital erythropoietic porphyria
3. Nonblistering photosensitivity
– Erythropoietic porphyria
– X-linked protoporphyria

below 12 g/dL (Venesection removes hepatotoxic liver iron which produces target organ damage). (b) Chloroquine – 125 mg b.d. enhances urinary clearance of porphyrin.

2. ***Erythropoietic porphyria*** – Pruritic urticarial swelling and redness of skin on exposure to sunlight, and severe burning sensation in affected parts. Hepatic involvement can lead to cirrhosis and liver failure. Protoporphyrin deposition may also cause cholelithiasis.

   Management – Oral β-carotene for solar sensitivity. Cholestyramine reduces plasma protoporphyrin levels and may slow activity of the liver disease.

3. ***Congenital porphyria*** – It is caused by a decrease in uroporphyrinogen cosynthase activity which results in overproduction of uroporphyrin I and coproporphyrin I. Symptoms usually commence during first few years of life. Skin reaction is severe and scarring on the hand may produce a claw-shaped deformity. Dystrophic nails may drop off. Lenticular scarring may lead to blindness. Teeth become brownish-pink due to their high porphyrin content.

   Management – Splenectomy and chloroquine therapy and hypertransfusion have ameliorating effect, but life expectancy is short.

INBORN ERRORS OF AMINO ACID METABOLISM

Maple Syrup Urine Disease

Can lead to severe illness and death in neonatal period. Symptoms and signs may be nonspecific and mimic those produced by other common disorders, e.g. birth asphyxia or infection.

Homocystinuria

Recessively inherited disorder of methionine metabolism caused by deficiency of the enzyme cystathionine synthase. Homocysteine and methionine accumulate in the plasma. Homocysteine interferes with cross-linkage in both elastic and collagen fibres impairing their natural strength.

Cause – Enzyme cystathionine synthetase which with co-factor vitamin B_6 controls union of serine and homocysteine to form cystathionine. The block results in accumulation of homocysteine and its excretion in urine.

Clinical features – (a) Skeletal – Osteoporosis involving vertebral bodies with kyphoscoliosis, deformities of thoracic cage, genu valgum and flat feet. Reduced mobility of joints, long fingers and toes and increase in height despite spinal curvature. (b) CVS – Myocardial infarction due to narrowing of arteries. Pulmonary embolism may occur. (c) Brain – Mental retardation and epilepsy. (d) Ocular – Iridodonesis followed by downward dislocation of lens with resultant glaucoma, buphthalmia and optic atrophy. (e) RS – Asthma may occur. Majority of children are disabled by age of 10.

Diagnosis – Positive cyanide-nitroprusside test in urine. Raised level of plasma methionine with low plasma cysteine.

Treatment – For pyridoxine responsive patients – Pyridoxine hydrochloride about 600 mg/day with slight restriction of protein. Also folic acid 5 mg/day. For pyridoxine resistant patient – Methionine 130–150 mg/day given in natural protein and cysteine 100–300 mg/day. Vitamins and minerals.

Phenylketonuria (PKU)

Cause – Deficiency of enzyme phenylalanine hydroxylase which catalyses conversion of phenylalanine to tyrosine.

Clinical features – usually appear after first year of life. Mental and growth retardation; eczema and pigment dilution, seizures, tremor, muscular hypertonicity, microcephaly, enamel hypoplasia and decalcification of long bones.

Diagnosis – Serum phenylalanine raised (>1.2 mmol/litre) with raised urinary phenylacetic acid and phenylpyruvic acid.

Treatment – Dietary restriction of phenylalanine to maintain blood level at 2.5–7.5 mg/100 mL (0.15–0.45 mmol/litre).

PKU VARIANTS – result from deficiency of pterin cofactors, essential not only for metabolism of phenylalanine, but also in synthesis of neurotransmitters, dopamine and serotonin. The disorders have been labelled 'malignant' PKU, as mental deterioration is not prevented by a low phenylalanine diet alone.

LYSOSOMAL STORAGE DISEASE

Mucopolysaccharidoses (MPS)

A group of inherited connective tissue disorders caused by deficiency of lysosomal hydrolases. There is accumulation of partially degraded mucopolysaccharide which interferes with normal function of various organs and leads to urinary excretion of these compounds and glycosoaminoglycans.

Clinical Presentation

1. ***Prominent dysmorphic features*** (MPS types I, II, VI)–
   a. Hurler's syndrome (Type H) – Progress slows towards end of first year. Clinical manifestations may include hepatosplenomegaly, herniae, dorsolumbar kyphosis, cardiac murmurs and corneal clouding. During second and subsequent years bone dysplasia (dysostosis multiplex) becomes more prominent leading to dwarfism. Steady progression of the multisystem abnormalities leads to death by 10 years of age.
   a. Hunter's SYNDROME (Type II) – Inherited as X-linked recessive. Features same as Hurler's but no corneal clouding, and progression at a slower rate.
2. ***Behavioural disturbance and dementia*** (MPS type III) – Developmental delay seen after second year of life. Gradual development of ataxia, progressive loss of mobility, and death in a vegetative state.
3. ***Severe bony abnormalities*** (MPS types IV and VI) – Short neck and trunk, barrel-shaped chest. Head appears to rest directly on thorax. Waddling gait and progressive genu valgum develops. Cardiac lesions, corneal clouding and deafness can occur.

   Diagnosis – Abnormal urinary excretion of glycosoaminoglycans in urine by electrophoresis.

CARBOHYDRATE METABOLISM

Glycogen Storage Disease (GSD)

A group of disorders in which the fine control of glycogen synthesis and catabolism is disrupted by an inherited enzyme deficiency resulting in normal or abnormal glycogen within the cell (GSD type O).

Von Gierke's disease

Cause – Due to absence of glucose-6-phophatase activity in liver, renal cortex, GI mucosa and platelets.

Clinical features – Hypoglycemia early in life. Hepatomegaly. Bleeding due to glycogen accumulation in platelets. Gouty arthritis. Others – Hyperlipidaemia, lactic acidosis, growth retardation and delay in pubertal maturation.

Diagnosis – Liver biopsy with assay of hepatic glucose-6- phosphatase activity.

Treatment – Frequent carbohydrate feedings or portacaval shunt procedures.

McArdle's Syndrome

Enzyme deficiencies are confined to skeletal muscles. Progressive muscle weakness with cramping pains on exertion. Muscle necrosis and myoglobinuria occurs in half the patients. Diagnosis from characteristic histological appearance of muscle, and enzyme assay.

Galactosaemia

A disorder due to accumulation of galactose and galactose-1-phosphate with resulting tissue damage.

Cause – Disturbance in conversion of galactose to glucose.

Clinical features – Widespread symptoms and signs. Child ill in first week of life with vomiting, failure to thrive. Jaundice and hepatomegaly. Cataracts in about 50%. May be hypoglycaemic. Prone to infection. Evidence of renal tubular dysfunction.

Diagnosis – confirmed by demonstration of absent enzyme activity.

Treatment – Omission of lactose and galactose from diet. Adequate proteins, calories and vitamins.

PURINE AND PYRIMIDINES

Lesch-Nyhan disease – Hereditary hyperuricemia with choreoathetosis, spasticity and mental retardation.

TRACE METAL METABOLISM

Wilson's disease.

LIPID METABOLISM

Familial hyper cholesterolaemia (Deficient LDL receptors).

12. AMYLOIDOSIS

A disorder of protein metabolism characterized by extracellular tissue deposits, localized or systemic, of an abnormal material, consisting of protein fibrils and also a glycoprotein known as amyloid P component (AP). Two main types of amyloid fibril are AL (amyloid light chain proteins) and AA (amyloid A fibril proteins). Clinical significance of amyloidosis depends on its type, and on the site of deposition.

Table 24 Classifies the most common types of amyloid and amyloidosis.

SYSTEMIC AMYLOIDOSIS

Table 25 lists the clinical features of systemic amyloidosis.

Clinical syndromes – based on chemical nature of fibril subunit proteins.

Table 24: Classification of the most common types of amyloid and amyloidosis

Type	*Fibril protein precursor*	*Clinical syndrome*
AA	Serum amyloid A protein	Reactive systemic amyloidosis associated with chronic inflammatory diseases
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis associated with myeloma, monoclonal gammopathy, occult dyscrasia
ATTR	Normal plasma transthyretin Genetically variant transthyretin	Senile systemic amyloidosis with local nodular amyloidosis, prominent cardiac involvement Familial amyloid polyneuropathy, usually with systemic amyloidosis Sometimes prominent amyloid cardiomyopathy or nephropathy
Ab_2M	β_2-microglobulin	Periarticular and occasionally systemic amyloidosis associated with kidney failure and long-term dialysis
Ab rare	β-protein precursor (and rare genetic variants)	Cerebrovascular and intracerebral plaque amyloid in Alzheimer's disease. Occasional familial cases
AIAPP	Islet amyloid polypeptide	Amyloid in islets of Langerhans in type II diabetes mellitus and insulinoma.

Table 25: Clinical features

Renal disease

Commonly
- Proteinuria
- Nephrotic syndrome
- Renal insufficiency
- Hypertension

Occasionally
- Microscopic haematuria
- Nephrogenic diabetes insipidus
- Renal tubular acidosis
- Renal vein thrombosis

Cardiac disease
- Restrictive cardiomyopathy
- Biventricular 'diastolic' failure
- Mimics constrictive pericarditis
- Rhythm disturbances
- Heart block
- Apparent angina, myocardial infarction

Respiratory tract disease
- Dyspnoea
- Haemoptysis
- Stridor
- Cough

Gastrointestinal disease
- Macroglossia (AL)
- Dysphagia
- Gastrointestinal haemorrhage
- Diarrhoea, constipation
- Malabsorption
- Intestinal perforation, obstruction
- Hepatomegaly
- Splenomegaly, rupture
- Skin disease

Commonly
- Purpura
- Plaques, papules, nodules

Contd...

Contd...

Renal disease
- *Occasionally*
- Scleroderma-like infiltration
- Alopecia
- Nail changes
- Bullous eruption

Nervous system
- Peripheral neuropathy
- Autonomic neuropathy and orthostatic hypotension
- Enlarged peripheral nerves
- Carpal tunnel syndrome

Musculoskeletal system
- Bone marrow (AL)
- May resemble rheumatoid arthritis
- Mono-arthropathy
- Bilateral glenohumeral infiltration with 'shoulder pads'
- Muscle infiltration
- Dialysis arthropathy syndrome (Ab_2M)

Miscellaneous
- Lymphadenopathy
- Goitre
- Isolated clotting factor IX and X deficiency
- Haemorrhage with normal clotting factors
- Sicca syndrome
- Adrenal involvement
- Involvement of subcutaneous fat

I. **Systemic amyloidosis** –

Reactive systemic (AA) amyloidosis – Associated with chronic infections, long-standing inflammatory disease e.g. RA and malignant neoplasms, e.g. myeloma. Usual clinical features are proteinuria, nephrotic syndrome and/or hepatosplenomegaly. Prognosis is poor.

Systemic AL amyloidosis – Usually in patients over 50, associated with multiple myeloma and lymphoma or as 'benign' monoclonal gammopathy (Bence-Jones protein). Liver, spleen, kidneys, nerves and gut are commonly involved. Cardiac involvement is in form of restrictive cardiomyopathy and intractable heart failure is the usual cause of death. Prognosis is worse than for AA amyloid.

Hereditary systemic amyloidosis – can manifest as predominantly neuropathic, nephropathic or cardiomyopathic form. *Familial Mediterranean fever* is a distinct group and is characterised by recurrent attacks of fever, polyserositis, arthritis and rashes, which generally resolve in a few days. A number of these patients develop systemic amyloidosis.

Senile systemic amyloidosis – Major deposits occur in the heart, but functional impairment is uncommon. Deposits may also occur in lungs, muscles and blood vessel walls. However, the cerebrovascular and intracerebral amyloid of 'normal' aged brains is distinct and derived from β-protein as in Alzheimer's disease.

II. **Localized amyloidosis** –

Senile amyloidosis – Deposits in heart, joints, seminal vesicles. No clinical significance as a rule.

Cerebral amyloidosis –

Alzheimer's disease is the most common form of dementia in older age groups and is characterized by the triad of cerebral amyloid angiopathy, neuritic amyloid plaques and neurofibrillary tangles.

Cerebral amyloid angiopathy is an uncommon cause of haemorrhagic stroke. The fibrils are derived from β-protein.

Prion disorders (e.g. Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome) are associated with an amyloid change in confirmation of the prion precursor protein (P_rP^C), which is a normal, widely distributed molecule. The altered amyloid form is proteinase resistant and is designated P_rPS^C. This material is the transmissible agent of the spongiform encephalopathies and may accumulate sufficiently to be identified histologically as amyloid. The change from normal autologous PP^c to pathogenic PP^c, which seems to occur by chance in sporadic prion disease, is promoted either by inoculation with exogenous P_rP^C or by genetic variants of P_rP^C .

Subacute spongiform encephalopathy (Creutzfeldt-Jakob disease, transmissible viral dementia, mad cow disease)

Transmission – Infection has been transmitted by consumption of beef from infected cows, from post-mortem and surgical specimens and corneal grafts, and to recipients of human growth hormone (obtained from human pituitary glands removed at autopsy).

Pathology – of CJD is very similar to bovine spongiform encephalopathy of cattle – status spongiosis (presence of 'bubbles and holes') in the cortex and sometimes in basal ganglia. Lesions are accompanied by marked fibrillary gliosis in later stages.

Clinical features – Abnormalities of personality and visual spatial coordination are generally first signs of illness. This is followed by a progressive severe dementia with myoclonus.

EEG – is initially normal but then develops sharp waves or spikes against a background of delta or theta slow wave activity.

CSF – is normal except for occasional mild elevation of protein.

Treatment – None. Death usually occurs within 2 years from onset of symptoms.

Kuru – A disorder confined to Fore people in highlands of New Guinea. It is characterized by cerebellar ataxia and a 'shivering tremor' which progresses to complete motor incapacity and death from intercurrent infection or malnutrition in less than one year after its onset. Dementia is not a feature.

Haemodialysis associated amyloid – Carpal tunnel syndrome, large joint arthropathy, lytic bone lesions, pathological fractures, soft tissue masses and tendinitis can complicate haemodialysis for end-stage kidney failure, from deposit of b_2M amyloid fibrils.

Endocrine amyloidosis – In APUD organs, APUDomas, medullary carcinoma of thyroid, and in islets of Langerhans.

Isolated massive nodular deposits – in skin, lung, urogenital tract.

Diagnosis

1. ***Biopsy*** – Full coagulation studies should be carried out to exclude factor X (and IX) deficiency before histological confirmation. Rectal biopsy is positive in majority of cases. Alternatives are labial gland biopsy and aspiration of fat from anterior abdominal wall. If negative, biopsy of organ suspected to be affected, e.g. liver, kidneys or heart. Histological examination is carried out under crossed polarized light after staining with alkaline alcoholic Congo red. Type of amyloid can be determined using immunohistochemical techniques on serum and urine.
2. ***Electrophoresis*** – and immunophoresis for presence of plasma cell dyscrasia. The monoclonal protein often consists of pure immunoglobulin light chains.
3. ***Radionuclide SAP studies*** – after IV injection of iodine-123 labelled serum amyloid O component (SAP). Characteristic visual patterns of amyloid can be

visualised after 24 hours in both systemic and localised amyloidosis, permitting the extent and distribution of deposits to be precisely identified.

Management

See Table 26.

13. HYPOTHERMIA

Hypothermia is a fall in core (rectal) temperature to <35°C.

CAUSES

- Prolonged exposure to cold or with slow cooling, e.g. accident while mountain climbing, fall into a crevasse, prolonged exposure to low temperatures in homeless individuals.
- Immersion and submersion in ocean, lakes, cold rivers.
- Any kind of snow accident, e.g. avalanches.

See Table 27 for risk factors of hypothermia

PATHOPHYSIOLOGY

1. Low temperatures cause the myocardium to become irritable and multiple rhythm and conduction disturbances appear, e.g. bradycardia, atrial fibrillation, ventricular arrhythmia and non-specific and specific, pathognomonic j-wave ECG changes. At temperature of <30°C ventricular fibrillation or asystole will occur.
2. Hypothermia induces hypokalaemia by shifting extracellular potassium into intracellular compartments. Extremely high potassium levels reflect transfer of cellular potassium to extracellular space indicate acidosis, cell lysis and tissue damage.
3. With profound hypothermia blood viscosity and haematocrit readings are increased primarily because of loss of intravascular fluid (plasma) into extravascular compartments leading to hypovolemia. Hyperviscosity also favours development of intravascular thrombi and coagulopathy.

CLINICAL FEATURES

Clinical features depend on severity of hypothermia (Table 28).

MANAGEMENT

Of profound hypothermia:

1. *Non-arrested patient* – Haemodialysis provides continuous blood flow rate of 300-450 ml per minute by using a percutaneous dual lumen venous access. Rewarming using forced hot air via a plastic blanket can be used as assisting device.
2. *Cardio-circulatory arrest* – (a) Extracorporeal blood rewarming by cardiopulmonary bypass (CPB) is an efficient method of rewarming and total body perfusion. (b) Extracorporeal circulation (ECC) – Main advantage of this method is the rapid institution by using groin access while closed chest compression continues.

Table 26: Reduction in fibril precursors protein production in systemic amyloid

Disease /Aim of treatment	*Example of treatment*
AA amyloid Suppress acute phase response	Immunosuppression in RA, Still's disease (chlorambucil) Colchicine for familial Mediterranean fever, surgery for osteomyelitis and uncommon cytokine-producing tumors
AL amyloid Suppress production of immunoglobulin light chains	Chemotherapy and stem cell transplantation for myeloma and monoclonal gammopathy
Hereditary amyloidosis Eliminate source of genetically variant protein	Orthotopic liver transplantation for variant transthyretin-associated familial amyloid polyneuropathy
Haemodialysis amyloidosis Reduce plasma concentration of β_2- microglobulin	Kidney transplantation

Table 27: Risk factors of hypothermia

- Children and old people
- Hypothyroidism and hypopituitarism
- Hypoglycaemia and adrenal Insufficiency
- Immobile or demented patient
- Drug overdose: Alcohol, hypnotic drugs.
- Trauma, sepsis, shock
- Hepatic or renal failure

Table 28: Clinical features of hypothermia

Mild 32–35°C	*Moderate 28–32°C*	*Profound <28°C*
Amnesia, apathy, impaired judgement. Peripheral vasoconstriction, greyish appearance, tachycardia Shivering	ECG changes, hallucinations, paradoxical undressing, loss of consciousness. Decline in pulse and cardiac output, arrhythmia, prolonged asystole. Hyporeflexia, rigidity, cessation of shivering	Coma. Fall in BP, bradycardia, diminished or absent peripheral pulses, VF, asystole. Apnoea, peripheral areflexia

3. *Treatment of complications*- includes treating arrhythmias class I and class III preferred.
4. Underlying disease needs to be corrected, e.g. hormone replacement in endocrine disease.

14. GENETICS

Two essential features of genetic information are that it is transmitted from generation to generation and that it varies between individuals of species. The understanding of the basic modes of inheritance is fundamental to genetic counselling and prenatal diagnosis.

TERMS USED IN GENETICS

Acquired chromosomal abnormality is derived from stem cells (e.g. the Philadelphia chromosome in CML) as a result of mutagenic or carcinogenic influences.

Allele – An alternative form of gene occupying the same locus on a particular chromosome.

Aneuploidy – The chromosome number is not an exact multiple of 23, e.g. trisomy and monosomy.

Base – The genetic information determining the amino acid sequence in peptide chains (the building blocks of proteins) is stored as the order of four bases adenine (A), guanine (G), cytosine (C) and thymine (T), which constitute each DNA strand.

Chromosome – A single DNA strand is <10 angstroms wide, but one human cell contains just under 2 meters of DNA. Each time a cell divides, this DNA must replicate itself completely and accurately, and the sets must separate quickly, and precisely into two daughter nuclei. This is accomplished by 'packing' the DNA, by coiling, recoiling and folding into discrete parcels known as chromosomes.

A normal human cell contains 46 chromosomes, comprising 23 pairs. In 22 (autosomes), the two members of a pair are almost identical in appearance (i.e. they are homologous). The remaining pair sex chromosomes are identical in females (XX), but of different length and staining characteristics in males (XY).

Chromosome constitution – The autosomes are numbered from the largest (1) to the smallest (22 in humans). The short arm of a chromosome is called 'p' and the long arm 'q'. The chromosome constitution of an individual is written with the chromosome number first, followed by the sex hormone constitution, followed by description of any abnormalities e.g.:

- 46, XY normal male
- 47, XX + 21 (common form of Down's syndrome, with an extra copy of chromosome 21, in a female)
- 46, XYt [(2; 19) p21; p12] (translocation between chromosomes 2 and 19, breaking at bands p21 and p12, respectively).

Codon – Three nucleosides code for a particular amino acid. Each of these triplets is called a codon.

Combination – Exchange of genetic information between DNA strands (e.g. between diploid chromosomes).

Constitutional chromosomal abnormality is present from early embryogenesis. It may be found in all tissues.

Contiguous gene syndromes involve loss of genes that may be functionally unrelated but are contiguous along the chromosome.

Deletion (del) – A section of chromosome (terminal or interstitial) is lost (a structural chromosomal abnormality).

Exons are sequences codons; they code for polypeptides.

Fragile site (fra) – A chromosomal site showing a tendency to break, producing a structural chromosomal abnormality.

Frameshift mutation is the change in code on usage which results when nucleotides are added to or deleted from a nucleic acid sequence, producing a novel translation of the code locus.

Genes comprise lengths of DNA containing sufficient codons to code for the amino acids in the polypeptide chain of a particular protein. Most genes comprise exons interspersed with introns of variable length which are often longer than the coding regions; for example, globin genes have two introns and three exons and collagen genes may have 50 introns.

Heterozygote – A diploid cell or organism in which the gene at a given locus is different on the two chromosomes.

Homozygote – A diploid cell or organism in which a given locus carries the same genetic variant at both sites.

Hybridization is the technique of using labelled, single-handed nucleic acid sequences (DNA probes) to identify complementary sequences. Use of the technique on an intact metaphase spread is termed in *situ* hybridization.

Introns are sequences of nucleotides that are non-coding.

Inversion (inv) is produced when two breaks occur in one chromosome and the middle piece is rotated by 180° and reinserted, producing a structural chromosomal abnormality.

Linkage is the inheritance of different genetic loci with a frequency greater than would be expected by chance alone.

Table 29: Common constitutional chromosomal syndromes

Syndrome	*Karyotype*	*Major clinical features*
Down's	47, + 21	Small head, round face, slanting eyes, epicanthic folds, short stubby fingers, mental retardation
Edwards'	47, + 18	Narrow face, characteristic facies, multiple internal anomalies, overlapping digits, high lethality, very severe handicap
Patau's	47, + 13	Midline craniofacial defects ranging from cyclopia to facial clefts, multiple anomalies, polydactylism, high lethality, very severe handicap
Fragile X (fra(X))	46, XX fra (X) 46, XY fra (X)	Characteristic breakage of Xq, mental retardation predominantly in males, macro-orchidism
Klinefelter's	43, XXX	Male hypogonadism, azoospermia, slightly decreased IQ
Turner's	45, XO	Short stature, amenorrhoea, renal and cardiac anomalies
	47, XYY	Above average stature, slightly decreased IQ
	47, XXX	Increased incidence of nonspecific behavioural disturbance, slightly decreased IQ
Balanced translocations		
Unbalanced translocations		Often mental retardation

Locus – The position of a gene or another well characterized sequence of DNA on a chromosome.

Microdeletion – A deletion too small to be seen by microscopy. Paradoxically, these may be 100s or 1000s of bases in size.

Mosaic individuals have two different cell lines in their constitution, usually as a result of a chromosomal abnormality arising during early cell division after fertilization.

Numerical chromosomal abnormality – Extra or missing chromosomes may occur; for example, trisomy 21 (Down's syndrome), monosomy X (Turner's syndrome).

Phenotype – Physical characteristics displayed by an individual.

'Ploidy' describes the number of chromosome sets:

- 23, haploid (one set)
- 46, diploid (two sets)
- 69, triploid (three sets)

Polymorphism is the existence of different versions of a characteristic in a population. Polymorphism may reflect genetic variation.

'Somy' refers to the number of copies of an individual chromosome per cell. Thus, the term 'trisomy' describes three copies (as in trisomy 21) and 'monosomy X' describes the absence of the second sex chromosome.

Splicing – Reconnection of DNA or RNA at specific sites after segments have been removed.

Structural chromosomal abnormalities include deletions, translocations and inversions. These may be inherited.

Tandem repeat variance – Segments of DNA comprising variable repetitions of short DNA sequences.

Translocation (t) – Two chromosomes break and exchange segments, producing a structural chromosomal abnormality.

Table 29 lists common constitutional chromosomal syndromes

MOLECULAR GENETICS

The human genome – contains as many as 50-100,000 genes varying in size. A typical gene is organized into regions of DNA that encode specific amino acids (exons) with larger regions of non-coding DNA (introns). The function of introns is largely unknown. The great variation in the size of genes mainly reflects differences in the number and size of introns.

Gene expression – In order to produce its protean product, a gene is transcribed and then translated.

Transcription: One strand of the DNA acts as a template for production of messenger RNA. This is then modified before leaving the cell nucleus to form the processed RNA molecule.

Translation: In the cytoplasm, mRNA is translated to form the gene product.

Regulation: In addition to exons and introns, the genome contains regions of DNA that flank genes and have an important role in regulation of gene transcription.

DNA analysis – The three commonly used methods for diagnostic molecular genetics are:

DNA hybridization: Double-stranded DNA is held together by the mutual attraction of paired bases mentioned earlier. *Uses* – (a) Detection of mutations in fragile X syndrome and myotonic dystrophy. (b) For characterizing chromosomal rearrangements and for microdeletions such as those occurring in DiGeorge and Prader-Willi syndromes.

DNA amplification involves producing many copies of a target sequence using PCR. It is fast and efficient and allows analysis of a particular sample (e.g. prenatal diagnosis) to be performed in 24–48 hours. Small amounts of tissue (e.g. a single hair root, a dried blood spot) can be

typed and even a single cell or gamete can be analysed. However PCR analysis can only be applied only to regions of DNA that have been cloned and sequenced.

DNA sequencing is used to determine the specific order of the bases in a given fragment of DNA. The procedure is semi-automated and data analysed by computer.

DNA markers – Human DNA shows much variation between individuals. This variation is the source of DNA markers which can be used to track diseases through families. Different types of variation give rise to different classes of DNA markers. (a) Restriction fragment length polymorphisms: RFLPs are of limited use, because each RFLP has only two forms (alleles). (b) Variable number tandem repeats – If a series of VNTR markers are used simultaneously, they produce a pattern of bands (a 'fingerprint') unique for every individual. This is the basis of 'genetic finger printing' which is used in forensic science and for paternity testing.

Linkage analysis. The first step in the search for the cause of genetic disorder is to identify the chromosome on which the faulty gene lies. This is achieved using linkage analysis, which follows the segregation of the disease and the DNA markers in a number of large families. When the marker and the disease are inherited together they are said to be linked; this is possible only if key individuals are heterogenous for the marker concerned (i.e. they have a different allele on each chromosome at a given locus).

Once the linkage is clearly established, closer markers can be isolated systematically until the gene itself can be sought. However, linkage analysis is often complicated by genetic heterogeneity, e.g. mutations in at least three different genes have been shown to cause retinitis pigmentosa.

Isolating the gene. Isolating and cloning a disease gene once it has been mapped is the most difficult problem in human genetics. Rarely, patients with a particular disease have chromosomal rearrangements that disrupts the disease gene, cloning the chromosome breakpoints and hence the disease gene is relatively easy.

Mutation analysis – There are three principal types of mutation that can cause loss or change of gene function:

Deletions/duplications – Part of a gene may be deleted, or more often duplicated. Deletions can be identified using PCR. About two thirds of cases of Duchenne muscular dystrophy are caused by partial deletions of the dystrophic gene. Deletions are identified by the absence of a PCR product because males have only one copy of the gene.

Base substitutions – Most changes do not alter restriction of enzyme sites, in which case the changes can be detected by a modification of PCR reaction in which primers for specific for normal and mutant alleles are used in separate reactions. Amplification in either reaction is indicated whether the normal or mutant allele is present.

Expanding trinucleotide repeats – This form of mutation is the cause of fragile X syndrome, myotonic dystrophy and Huntington's disease. In these disorders, normally polymorphic trinucleotide repeat sequences at the disease location expand in affected individuals beyond the normal size range. The simplest method of detection is to amplify across the expanding region.

Mendelian disorders

Single gene defects – Result from single abnormal gene of major effect. Those carried on X chromosome are usually recessive, those on the autosomes, dominant or recessive. A dominant mutation implies that the disorder is manifest in a heterozygous state. A recessive mutation requires a homozygous state to manifest clinically.

1. ***Autosomal dominant (AD) traits*** – Autosomal genes are located on chromosomes other than sex chromosomes. The genotype of such a trait may be AA both dominant alleles homozygous state or Aa one dominant allele – heterozygous state (allele is an alternative form of a gene occupying the same locus on a particular chromosome). Each affected individual must have at least one parent suffering from the disease, and he/she will transmit the disorder vertically to 50% of the offspring. Both males and females are equally affected. These disorders often have a delayed age of onset and vary in severity of manifestations.
2. ***Autosomal recessive (AR) traits*** – The genotype is a two recessive alleles – (homozygous state). The parents are often normal (heterozygotes) and only siblings are affected. An affected individual may transmit the disorder to all, one half or none of the offspring depending on whether he marries another affected individual, a heterozygous carrier, or a normal person respectively. Unlike AD disorders, these generally manifest early in life and have a uniform degree of expression.
3. ***X-linked dominant (XLD)*** – The genotype is 46XY or 46XX where X is the dominant mutant gene. Females to male ratio is 2:1. An affected male will transmit the anomaly to all his daughters but not to sons (who inherit his Y chromosome). A heterozygous female transmits the disorder to half her offspring (both sexes).
4. ***X-linked recessive (XLR)*** – vary from mild to severe. The genotype is 46XY or 46XX, where X is the recessive mutant gene. Usually males are affected, a female

suffers only when she is homozygous for the recessive allele. An affected male does not transmit the disorder to any of the sons, but the abnormal gene is transmitted to all his daughters (who may be carriers if the mother is normal or may manifest the disease if mother is a carrier or is affected by the disease). A carrier female transmits the disease to half her sons or to half her daughters.

5. ***Y-linked inheritance*** – Some male Mendelian disorders require exposure to an environmental factor usually a drug, to manifest (pharmacogenetic disorders) e.g. slow acetylation of isoniazid (inherited as AD trait) can cause polyneuritis, G6PD deficiency on exposure to certain drugs, malignant hyperthermia (inherited as AD trait).
6. ***Heterogenicity or variable modes*** – Some clinically similar diseases may be inherited in different ways, e.g. Mucopolysaccharidoses (AR, XLR). Ehlers-Danlos syndrome (AD, AR, XLR). Polycystic disease of kidneys (AD, AR). Retinitis pigmentosa (AD, AR, XLR). Ichthyosis (AD, XLR). Deafness (AD, AR, XLR). Spinocerebellar ataxias (AD, AR, XLR), Muscular dystrophies.

Multifactorial genetic disorders – including congenital malformations. Here both environmental and genetic factors combine in varying proportions in different individuals, even within the same family, to reach the threshold beyond which abnormality appears. It is possible to identify candidate genes, such as those encoding the apolipoproteins and the low density lipoprotein involved in cholesterol metabolism. Population studies may then reveal the inheritance of a particular set of these genes (haplotype) which can be correlated with a higher risk of coronary artery disease.

Diseases – (a) *Congenital* – Congenital heart disease, neural tube defects, congenital pyloric stenosis, cleft lip/and/or cleft palate, congenital dislocation of hip. (b) *Adult life* – Diabetes mellitus, IHD, peptic ulcer, essential hypertension, epilepsy, psychoses.

Disorders with mitochondrial inheritance – The mitochondrial DNA (which is of male origin) may transmit traits in a manner that does not follow Mendelian principles. The trait is passed on from a mutant mother to her offspring but not from a mutant father to his children. Examples are Leber's optic atrophy and ragged red fibre myopathy.

Genetic heterogenicity and pleiotropism – Genetic heterogenicity means that a particular phenotype (physical characters displayed by an individual) can result from anyone of separate genotypes, e.g. Marfan's syndrome and homocystinuria are both associated with similar manifestations of subluxation of ocular lenses and skeletal abnormalities. The genotypes, mode of inheritance and prognosis of the two are however different.

Pleiotropism means that a single gene can result in several phenotypic features, e.g. association of melanin spots of buccal mucosa, lips, and digits with jejunal polyps in Peutz-Jegher syndrome.

See Table 30 for mendelian disorders and Table 31 for prenatal diagnosis

Gene therapy – is the introduction of healthy genes into patients to replace their own defective genes. This concept of delivering genes to specific targets has widened the field from treatment of single-gene defects (e.g. cystic fibrosis and DMD) to alleviation of multigene defects (e.g. neurodegenerative disease, cardiac disease).

Table 30: Mendelian disorders

Autosomal dominant	
Marfan syndrome	Polycystic kidney disease
Tuberous sclerosis	
Achondroplasia	Polyposis coli
Familial hypercholes-terolaemia	Acute intermittent porphyria
Huntington's chorea	Facioscapulo-humeral m. Hereditary
Neurofibromatosis	Dystrophy
Dystrophia myotonica	Spherocytosis
Autosomal recessive	
Sickle cell anemia	Glycogen storage disease
β-thalassaemia	
Cystic fibrosis	α-antitrypsin deficiency
Phenylketonuria	Haemochromatosis
Galactosaemia	
Tay-Sach's disease	
Scapulohumeral m. dystrophy	
Wilson's disease	
X-linked dominant	
Vitamin D-resistant rickets	
Pseudohyperparathyroidism	
X-linked recessive	
Haemophilia	Fabry's disease
G6PD deficiency	Colour blindness
Duchenne muscular dystrophy	Nephrogenic
	Diabetes insipidus
Menke's syndrome	Lesch-Nyhan syndrome
Testicular feminization	

Table 31: Prenatal diagnosis

Technique and timing		Types of disorders detected
Chorionic villous sampling (CVS)	Transcervical 9–11 weeks Transabdominal 12–16 weeks	*Direct analysis of uncultured chorionic villi —* Trisomic Down's syndrome and other numerical chromosome abnormalities. Translocation Down's syndrome. Inherited metabolic disorders by enzyme assay. Many single gene defects by DNA analysis. Foetal sexing for X-linked recessive disease.
		Cultured cells from chorionic villi — All chromosome abnormalities. Inherited metabolic disorders. Many single gene defects by DNA analysis.
Maternal serum α-fetoprotein	16–19 weeks	Raised – Neural tube defects. Lowered – Down's syndrome, Edwards's syndrome.
Amniocentesis	16–18 weeks	*Amniotic fluid cell culture —* All foetal chromosome abnormalities, including Down's syndrome. Many metabolic defects by enzyme assay. Many single gene defects by DNA analysis. Foetal sexing for X-linked recessive disease. *Amniotic fluid supernatant –* *α-fetoprotein and α-acetylcholine esterase assays* Open spina bifida and encephaly. Anterior abdominal wall defects. Congenital nephrosis. *Alkaline phosphatase and α-Glutamyltranspeptidase assay –* Cystic fibrosis. *Other biochemical assays –* Congenital adrenal hyperplasia. Mucopolysaccharidoses.
Foetal blood sampling	18 or more weeks	Inherited immunodeficiencies Platelet disorders Foetal viral infections Chromosome aberrations Haemoglobinopathies. Haemophilia A and B Rapid foetal chromosome analysis in pregnancies at risk for fragile X syndrome of mental retardation, or in pregnancies in which ultrasound has revealed features suggestive of a chromosomal syndrome. For confirming equivocal CVS and amniocentesis results.
Ultrasonography	16–18 weeks	Certain types of skeletal dysplasia – Spina bifida, short limb dwarfism, polydactyly, osteogenesis imperfecta. Severe congenital heart disease. Infantile polycystic disease of kidney, renal agenesis, bladder outflow obstruction. Anterior abdominal wall defects. Hiatus hernia. Duodenal atresia.
Foetoscopy and foetal syndromes tissue sampling	after 18 weeks	*Endoscopic visualization of foetal structures* – for diagnosis of dysmorphic associated with facial or limb defects not easily identified by ultrasound. *Foetal skin biopsy* – Skin conditions, e.g. epidermolysis bullosa, ichthyosis, albinism.
		Foetal liver biopsy – Rare metabolic disorders.
Maternal serum screening syndromes,	16–20 weeks	Raised maternal serum AFP levels in open neural tube defects (about 90%). Remainder include anterior abdominal wall defects, chromosomal (trisomies 18 and 13), teratomas, congenital nephrosis, haemangioma of placenta or cord, cardiac monster and hereditary persistence of AFP.

Gene delivery

1. Virus-mediated delivery –
   a. *Retroviruses* – The wild-virus type is disabled by deleting essential genes so that infection cannot occur without a helper virus. In patients with familial hypercholesterolemia, a normal low density lipoprotein gene can be introduced into liver cells to reduce the serum cholesterol level.
   b. *Adenoviruses* – have been used for treatment of cystic fibrosis and for introduction of genes into CNS.
2. Non-viral therapy – (a) Liposomes. (b) DNA-receptor complexes. (c) High-energy bombardment of tissue. (d) Direct DNA uptake.

Gene therapy for cancer – (a) Introduction or interleukin-2 (a T cell activator) into a patient's T lymphocyte and reintroduction of these primed cells back into the patient can shrink some cancers (e.g. melanomas). (b) Introduction of a suicide gene into the cell, e.g. the introduction of the enzyme thymidine kinase under the control of α-fetoprotein promoter will result in production of cytotoxic drug in the tumour but not in normal cells.

15. SLEEP DISORDERS

PHYSIOLOGY OF SLEEP

Sleep is a result of activity in certain sleep-provoking areas in the brainstem. States and stages of sleep are defined on the basis of typical EEG, electrooculogram (EOG a measurement of eye-movement activity), and the EMG (see Table 32).

Table 32: Types of sleep and their differentiation

Features	*Rapid-eye movement (REM) sleep*	*Non-rapid eye-movement (NREM) sleep)*
Eye-movement	Rapid conjugate	No eye-movement
Temp; BP, heart rate, resp.	Fluctuate	No fluctuation
Muscle twitching	Absent	Present
Site of origin	Pontine reticular formation	Midline pontine and medullary nuclei
Mediated by	Noradrenaline	Serotonin
Investigations		
EEG	Low voltage, fast activity	High voltage with slow activity (deep sleep)
EOG	Rapid, conjugate	Absent
EMG	Absent	Reduced

Periods of NREM and REM sleep alternate cyclically through the night at intervals of 60–120 minutes.

CLASSIFICATION OF DISORDERS OF SLEEP

I. **Dyssomnias** –
   1. ***Intrinsic sleep disorders*** –
      a. Narcolepsy – Tetrad of excessive daytime somnolence, cataplexy (sudden loss of postural tone precipitated by emotion), hypnogogic hallucinations at onset of sleep or upon awakening (hypnopompic hallucination), sleep paralysis (on awakening patient is unable to move for 2–3 minutes).

         Treatment – Drugs which inhibit REM sleep such as amphetamine or better methylphenidate or pemoline. Tricyclic anti-depressants for cataplexy, hallucinations and sleep paralysis.
      b. Psychophysiological insomnia – A behavioural disorder in which there is a preoccupied perception of inability to sleep at night, initially triggered by a stressful event.
      c. Sleep apnoea – (OSA) is a part of a spectrum of sleep-disordered breathing characterised by repetitive episodes of partial or complete obstruction of upper airways during sleep, commonly associated with hypoxia and usually terminated by arousal from sleep, resulting in sleep fragmentation and deleterious effect on day time functioning. OSA in association with daytime symptoms such as sleepiness is termed 'OSA syndrome'. An overnight sleep study (polysomnography) is the standard investigation in diagnosis of OSA and other sleep disorders, and in the titration of nasal continuous positive airway pressure (CPAP) therapy.

         Treatment – (i) General measures such as avoidance of alcohol or sedatives, weight loss, reduction of nasal resistance. Treatment of underlying cause such as hypothyroidism. (ii) Continuous positive airway pressure (CPAP) in severe cases. (iii) Surgery – Removal of enlarged tonsils or other obstructive tumours.
      d. Restless leg syndrome.
      e. Periodic limb movement disorder (nocturnal myoclonus)
   2. ***Extrinsic sleep disorders*** –
      a. Adjustment sleep disorders – e.g. changes in sleeping environment, anxiety, after an illness.
      b. Altitude insomnia – Exposure to high altitude may give rise to Cheyne-Stokes type of periodic breathing during NREM sleep, but regular breathing pattern during sleep.

c. Drug-induced sleep disorders – Caffeine, amphetamine, rebound insomnia associated with sudden withdrawal of hypnotics. Levodopa, corticosteroids, theophylline, thyroid hormone.

d. Circadian sleep disorders – Jet-lag syndrome, shift-work insomnia.

II. **Parasomnias** – Behavioural disorders during sleep associated with brief or partial arousals but not marked disruption of sleep.

1. ***Arousal disorders***

a. Sleep walking (Somnambulism) – Varies from sitting up in bed to walking around the house. Episodes occur during deep or intermediate REM sleep.

b. Night terrors (Pavor nocturnus) – Child wakes up in a state of fright, with tachycardia and sweating.

c. Sleep enuresis – Bedwetting beyond age of 5-6 years considered abnormal and part of parasomnia manifestation. Treatment mainly consists of badder training exercise and medication consists of oxybutynin and imipramine.

2. ***Sleep-wake transition disorders*** – Nocturnal leg cramps, sleep talking.

a. Parasomnias usually associated with REM sleep – Nightmares, sleep paralysis, sleep-related penile erections. Behavioural disorders usually in middle aged or old men with violent behaviour during sleep sometimes with self-injury.

Treatment- Clonazepam 0.5–2 mg

b. Other parasomnias – (a) *Sleep bruxism* or teeth grinding usually in young adults with risk of dental injury. (b) *Nocturnal enuresis.*

III. **Sleep disorders with systemic or physiological illness** –

1. ***Mental disorders*** – Anxiety, depression, obsessive-compulsive disorders. Chronic alcoholism.

2. ***Neurological disorders*** – Parkinsonism, cerebral degenerative diseases, sleep-related epilepsy, sleep-related headache (migraine, cluster headache), fatal familial insomnia (hereditary disorder due to degeneration of nuclei in thalamus).

3. ***Miscellaneous medical diseases*** – COPD, CHF, hiatus hernia, peptic ulcer, cervical spondylosis, backache, sleeping sickness.

16. PHAKOMATOSIS

A group of hereditary disorders characterised by multi-organ malformations and tumors, also designated as neurocutaneous syndrome because of neurological and cutaneous involvement.

CLINICAL PRESENTATION

1. ***Neurofibromatosis*** (von Recklinghausen's disease) – inherited as AD.

a. Cafe-au-lait spots – Brown macules on trunk (Must be 5 or more with at least one having a long axis >1 cm to be significant).

b. Neurofibromas – along peripheral nerves and increasing with age.

c. Mollusca fibrosa – Large, pedunculated, pinkish cutaneous fibromas.

d. Plexiform neuromas – Diffuse neurofibromatosis with skin and subcutaneous overgrowth and occasional underlying bony abnormality.

e. Skeletal – Kyphoscoliosis, macrocephaly, spina bifida, pes cavus and syndactyly.

f. CNS – (a) Mental retardation. (b) Epileptic seizures (c) Neoplasms – (i) Cranial nerves particularly VIII, V and II. (ii) Intraspinal (iii) Peripheral nerves. Some neurofibromata may become sarcomatous.

g. Hypertension.

h. Retinal phakomas may be seen.

2. ***Tuberous sclerosis*** – AD condition. *Clinical features* – due to masses of glial tissue in various organs.

a. Skin – Adenoma sebaceum – Papular rash like severe acne on butterfly area of face. Also lipomas, depigmented naevi and fibromas underneath the nail.

b. Neurological – Mental retardation, seizures. Intracranial neoplasms may cause obstructive hydrocephalus. CT scan may show calcium deposits in periventricular areas.

c. Renal cysts and tumours may occur.

3. ***Sturge-Weber syndrome*** –

a. Port wine stain (capillary naevus) over one or more divisions of fifth cranial nerve, usually the first.

b. Eye involvement – Glaucoma, choroidal angioma.

c. Neurological – Epileptic seizures, hemianopia, mental retardation and behavioural disorders.

d. Skull X-ray – Typical 'tramline' calcification due to deposits of calcium in middle layers of cerebral cortex.

4. ***Ataxia telangiectasia*** (Luis-Barr syndrome) – AR condition characterised by mild cerebellar syndrome, or choreoathetotic movements in early childhood. After the age of 4 or 5 telangiectasias appear on face, bulbar conjunctiva and limbs, progressing as the child grows older. Respiratory tract infections common, associated with diminution of IgA and IgE.
5. ***von Hippel-Lindau disease*** – Autosomal dominant disorder characterised by haemangioblastoma of the neuraxis and cysts in kidney, liver and pancreas.

Clinical features – (a) Cerebellar – Progressive ataxia. (b) Spinal cord – Cord or root compression. (c) Retinal haemangioblastoma seen on fundoscopy. (d) Erythrocytosis – from excessive production of erythropoietin. (e) Pheochromocytoma and renal carcinoma may occur.

17. OCULAR MANIFESTATIONS OF SYSTEMIC DISEASE

Neurological disorders: Most neurological disorders present with visual dysfunction (e.g. loss of vision, diplopia).

1. **Ocular vascular disease**
   a. *Central retinal artery occlusion* – Sudden, usually painless, monocular blindness. If occlusion is temporary, patient may complain of transient monocular visual loss (amaurosis fugax). Permanent occlusion leads to retinal infarction and blindness. However, if only a branch retinal artery is occluded there may be an altitudinal field defect. Fundoscopy may demonstrate embolic material within blood vessels, retinal oedema and later a cherry-red spot.
   b. *Anterior ischemic optic neuropathy* – from infarction of optic nerve head due to occlusion of posterior ciliary arteries. There is sudden, painless, monocular visual loss, usually altitudinal. Disc is swollen and pale, there may be haemorrhages and cotton-wool spots.
2. **Optic neuropathies** – Non-vascular optic neuropathies usually present as monocular visual disturbance with central scotoma, impaired colour vision and relative afferent pupillary defect. Causes – Optic neuritis, compression of optic nerve. by retrobulbar masses (e.g. tumours or connective tissue swellings as in Grave's disease), metabolic (e.g. vitamin B_{12}, B_6 or B_1 deficiency), drugs or toxins (e.g. ethambutol, isoniazid, lead).

   Tobacco-alcohol amblyopia is optic neuropathy caused by tobacco, alcohol or nutritional deficiencies (e.g vitamin B_{12}, B_6 or B_1).

   Optic neuritis – resulting from demyelination is the most common cause of acute optic neuropathy. It presents as progressive visual loss after a few days, improving during subsequent weeks. It may be associated with a dull ache of the eye, exacerbated by eye movement. The optic disc may be swollen (papillitis) or appear normal (retrobulbar neuritis).
3. **Optic disc swelling** – may result from local optic nerve. pathology (e.g. inflammation, infiltration, meningioma). Swelling caused by raised intracranial pressure is termed papilloedema. Visual acuity is reduced in optic nerve pathology, but is normal in papilloedema. In papilloedema the blind spot is enlarged because the optic n. head swells.

   Raised intracranial tension – consists of papilloedema and increased intracranial pressure. It usually occurs in obese, young women who present with headache and sometimes transient visual obscuration. There is an association with use of oral contraceptives, corticosteroids and several antibiotics including tetracycline. Also dural sinus thrombosis.
4. **Optic chiasm, tract and radiation lesions** – have been described in Chapter 6. Table 33 summarises localization of afferent visual pathway lesions.
5. **Ophthalmoplegia**

Table 33: Lesions in visual pathway

	Optic n.	*Optic chiasm*	*Optic tract*	*Temporal lobe*	*Parietal lobe*	*Occipital Lobe*
Acuity	N/-	N	N	N	N	N
Colour vision	–	N/-	N/-	N	N	N
Afferent pupil defect	+	+	+	–	–	–
Disc pallor	+/-	+/-	+/-	–	–	–
Visual field defect	Central scotoma	Bitemporal	Homon. (incongr.)	Homon. sup.	Inf.	Homon.

External ophthalmoplegia is paralysis of external ocular muscles. Causes – Infranuclear (myasthenia gravis, mass lesions within the orbit, cavernous sinus or near brainstem), nuclear (vascular disorders or demyelination affecting brainstem nuclei), of IIIrd, IVth or VIth ns.), or supranuclear (frontal infarcts).

Internal ophthalmoplegia refers to paralysis of sphincter pupillae and ciliary muscles. Causes – Small pontine infarct, in younger patients demyelination is more often responsible for bilateral internuclear ophthalmoplegia. Clinical features. – In right internal ophthalmoplegia when patient attempts to look to the left, abduction of right eye is normal, but right eye is unable to adduct, because the right medial rectus is not activated in concert. The left eye usually displays jerk nystagmus and convergence to a near stimulus may be preserved.

Endocrine disorders

Hypothyroidism – may be lental opacities, blepharospasm, keratoconjunctivitis.

Hyperparathyroidism – Conjunctival flare, corneal calcification.

Tumors of adrenal medulla (Neuroblastoma) – Unilateral or bilateral proptosis, accompanied by orbital swelling in temporal region, ecchymosis of eyelids, and papilloedema in some cases.

Metabolic disorders

Diabetes mellitus – Cataract – Incidence of senile cataract is higher. Retinopathy – (a) Background or non-proliferative – microaneurysms, haemorrhages, hard exudates, venous dilatation. Background retinopathy may progress to proliferative retinopathy or maculopathy. (b) Proliferative retinopathy – Intraretinal microvascular abnormalities (IRMA), venous abnormalities, cotton-wool spots and clusters of haemorrhages. (c) Maculopathy – is the most common cause of visual loss in type 2 DM, and can be exudative or oedematous, or ischemic. Advanced diabetic eye disease includes preretinal and vitreous haemorrhages and rubeotic glaucoma, a painful complication that results from extensive retinal ischemia. (d) Cranial n. affection – Optic, oculomotor, trochlear or abducent nerves.

Inborn errors of metabolism – (a) Corneal haziness or clouding in Hurler's, Morquio's, and Scheie's and beta-glucuronidase syndromes. Tapetoretinal degeneration in Hunter's and Sanfilippo's syndromes. (b) Pigmentation of conjunctiva and sclera in alkaptonuria. (c) Albinism – Translucent iris, nystagmus, photophobia and hypoplasia of the foveae.

Amyloidosis – Hypertrophied conjunctivitis (especially following trachoma), purpura of eyelids, ptosis, nodules in conjunctiva and sclera and vitreous opacities.

Hyperlipoproteinaemia – Lipaemia retinalis, arcus senilis (small retinal vessels appear paler).

Sphingolipidoses – Gaucher's syndrome: Deposits in conjunctiva and sclera.

Tay-Sachs' disease and Niemann-Pick syndrome – Cherry-red macula.

Disorders of mineral metabolism – (a) *Calcium* – Hypo- and hyperthyroidism have been discussed. (b) *Copper* – Chalcosis (deposits in conjunctiva), 'sunflower' cataract, Kayser-Fleischer ring. Iron particles retained in the eye may cause siderosis bulbi, Fleischer's ring (hemosiderin ring round the base of the cone) and Stahli-Hudson line (linear brown pigmentation in cornea).

Systemic infections

Tuberculosis – (i) Orbit: periostitis, rarely tuberculoma with fistula formation. (ii) Tarsitis, dacryoadenitis and dacryocystitis. (iii) Conjunctiva – Allergic (phlyctenular lesion) or infective. (iv) Cornea: Phlyctenular keratoconjunctivitis. Rarely deep keratitis, tuberculous infiltrates and ulcers. (v) Episcleritis, scleritis and keratoscleritis. (vi) Uveal tract: Anterior: Granulomatous iritis, nodular iritis, miliary tubercles on iris or conglomerate tubercle of anterior segment. Posterior: Circumscribed choroiditis, disseminated choroiditis, choroid tubercles miliary or solitary, or tuberculoma. (vii) Retina: Periphlebitis.

Leprosy: (i) Leproma of sclera. (ii) Cornea: Sclerokeratitis. (iii) Subepithelial punctate keratitis. (iv) Interstitial stromal keratitis. (v) Thickening of corneal nerves. and of Descemet's membrane. (vi) Leproma nodules (pearls) at the pupillary borders of the iris, singly or in groups.

Syphilis – (a) Interstitial keratitis. Also keratitis pustulo formis profunda and deep punctate keratitis. (b) Episcleritis and scleritis occasional. (c) Iritis and iridocyclitis, iris atrophy, syphiloma of ciliary body and iris. (d) Choroiditis (more often in congenital syphilis). (e) Visual pathways – Papilloedema, papillitis and optic atrophy. (f) 3rd and 6th cranial ns. involvement. (g) AR pupil, fixed pupil.

IE – Haemorrhages in retina and conjunctiva, Roth's spots.

Diphtheria – Extrinsic nerve. palsies and paralysis of accommodation.

Whooping cough – Subconjunctival hemorrhage.

Parasitic infections

Malaria – Pigmentation of conjunctiva and retinal haemorrhages.

Toxoplasmosis – (a) Congenital: Posterior uveitis from activation of quiescent cysts. (b) Chorioretinitis leading to circumscribed glial scar.

Cysticercosis – (a) Cysts in subconjunctival tissue, orbit or AC. Vitreous humor cysticercus may cause exudative uveitis and endophthalmitis. (b) Retinal tear from cysticercus.

Leptospirosis – Photophobia, ocular pain, conjunctival suffusion or hemorrhage.

Haematological conditions

Haemoglobinopathies – Dilatation and tortuosity of retinal vessels, retinal haemorrhages, retinal micro-aneurysms and vitreous haemorrhages.

Polycythemia – Engorged conjunctival and episcleral vessels. Dusky fundus with dilated, tortuous and violaceous veins.

Dysproteinemia – (a) Macroglobulinemia: Sludging of conjunctival circulation, haemorrhages, cotton-wool type exudates, retinal oedema and venous occlusion. (b) Cryoglobulinemia – Retinal haemorrhages, exudates, arterial narrowing, venous thrombosis.

Helminthic infections

Ankylostomiasis – Lid oedema, retinal haemorrhages (from anemia), stellate retinopathy (due to toxic effect), granuloma in vitreous and retina.

Ascaris – Haemorrhages, granulomatous uveitis and oedema (due to direct invasion). Lid oedema and phlyctenulosis due to allergy.

Guinea worm – may be detected in eyelids, conjunctiva and orbit.

Hydatid disease – Cysts may invade the eye or orbit.

Onchocerciasis – Keratitis, microfilaria in AC and vitreous, uveal inflammation, degeneration and atrophy of retina.

Collagen diseases

Rheumatoid arthritis – Refer

SLE – Transient cotton-wool type exudates in macular region. Retinal haemorrhages and oedema, conjunctivitis, episcleritis, keratitis and iridocyclitis.

Polyarteritis nodosa – Scleritis and episcleritis, corneal ulcer, uveitis, retinal exudates and haemorrhages, ocular palsy. Occlusion of central retinal artery may occur.

Progressive systemic sclerosis – Cataract.

Dermatomyositis/polymyositis – Oedema and erythema of eyelids, extrinsic muscle involvement, retinal haemorrhages and exudates.

Wegener's granulomatosis – Proptosis, chemosis, ocular motility impairment and papilloedema.

Diseases of muscles

Myasthenia gravis – Ocular muscles are first to be involved, with resultant ptosis or double vision. Lid twitching.

Ocular myopathy – Progressive external ophthalmoplegia.

Myotonia atrophica – Cataract, bilateral ptosis.

Skin and mucous membrane affection

Muco-cutaneous lesions – Benign mucosal pemphigoid (ocular pemphigus, shrinkage of conjunctiva), pemphigus, erythema multiforme, Reiter's syndrome, Behcet's syndrome, dermatitis herpetiformis, epidermolysis bullosa.

Dermatoses – Rosacea, seborrhoea, eczema, ichthyosis, xeroderma pigmentosum, psoriasis vulgaris, keratosis follicularis.

Vitamin A deficiency – *Signs:* (a) *Primary* – Conjunctival xerosis, Bitot's spots, corneal xerosis, corneal ulceration with xerosis, keratomalacia. (b) *Secondary* – Night blindness, xerophthalmia fundus, corneal scars following keratomalacia.

18. STEM CELL THERAPY

Stem cells are defined as "cells that have clonogenic and self-renewing capabilities and that differentiates into multiple cell lineages"

Characteristi features include

1. Undifferentiated cells
2. Ability for unlimited self-renewal.
3. Infrequent proliferation.
4. Replenish progenitor cells.

TERMINOLOGY

Potency: Some of developmental options available to cell:

- Totipotent: Ability to (re)generate an organism in total. In mammals only the zygote and first cleavage blastomere are totipotent.
- Pluripotent: Ability to form all lineages of body, e.g. embryonic stem cells.
- Multipotent: Ability of adult stem cells to form multiple cell types of one lineage, e.g. haemopoietic stem cells.
- Unipotent: Cells from one cell type, e.g. spermatogonal stem cells (can only generate sperms).

Table 34: Stem cells

Intrinsic or Endogenous	Extrinsic
Basal epithelial	
Cells in trachea and larger airways	Adult stem cells
	Embryonic stem cells
Clara cells in smaller airway	
Type II	
Pneumocytes in lung parenchyma	

CLASSIFICATION OF STEM CELLS

Embryonic stem cells – Cells isolated from the inner mass of early developing blastocytes. Embryonic stem cells have the capacity for self-renewal and are pluripotent, having the ability to differentiate into cells of all embryonic lineage and all adult cell types. However, they cannot form extra embryonic tissues such as trophectoderm.

Adult stem cells – Cells isolated from adult tissues including bone marrow, adipose tissue, skin, umbilical and blood and placenta that have the capacity for self-renewal. In general, adult stem cells are multipotent, having the capacity to differentiate into mature cell types of the parent tissue. Some adult stem cells such as mesenchymal stem cells exhibit a large range of differentiation that is not limited to a single tissue type.

Adult tissue-specific stem cells – The same as adult stem cells but with defined tissue specificity. A relatively undifferentiated cell within a given tissue that has the capacity for self-renewal through stable maintenance within a stem cell niche. Adult tissue specific (endogenous) stem cells have a differentiation potential equivalent to the cellular diversity of the tissue in which they reside. The haemopoietic stem cells the prototypical adult tissue stem cells.

Progenitor cells – A collective term used to describe any proliferative cell that has the capacity to differentiate into different cell lineage within a given tissue. Unlike stem cells, progenitor cells have limited or no self-renewal capacity. The term "Progenitor cell" is commonly used to indicate a cell that can expand rapidly but that undergoes senescence after multiple cell doubling (see Table 35 and 36).

Table 35: Indications of stem cell therapy

• GI conditions
Achalasia (endoscopic intrasphincteric injection)
• Cardiovascular diseases
Coronary artery disease
Dilated cardiomyopathy
Congestive heart failure
Myocardial infarction
Primary pulmonary hypertension
Peripheral arterial diseases
• Lung disease
Interstitial lung disease
Acute respiratory distress syndrome
Cystic fibrosis
Pulmonary arterial hypertension
Lung cancer
• Neurological disorders
Multiple sclerosis
Parkinson's disease
Alzheimer's disease
Muscular dystrophy (intrathecal of autologous derived bone marrow stem cell)
Stroke
• Spinal cord injuries and nongenetical neurological disorders
Paraplegia
Cerebral palsy
Post traumatic spinal cord injury
• Orthopaedic conditions
Cartilage damage
Sport injury
Bone cysts
Osteoarthritis
Avascular necrosis
Nonunion fracture
Bone regeneration
• Infertility management
Degenerative/poor endometrial development
• Asherman's syndrome
Aesthetic/cosmetic therapies
Stable vitiligo
Face lifting/wrinkles
Breast augmentation
Hair generation
• Dermatological conditions
Diabetic foot ulcer
Nonhealing ulcers
Burns and wounds
Postinflammatory hypo-or depigmentation
• Organ transplantation
Graft versus host disease
• Kidney disease
Acute kidney injury
Chronic kidney disease
Lupus nephritis

Table 36: List of stem cells

Type	*Advantages*	*Disadvantages*
Embryonic blastocysts (inner cell mass)	Totipotent and highly expandable	Immunosuppression required, ethical debate, lack of availability and tumour potential
Umbilical Cord Blood Cells (Umbilical cord)	Pluripotent and highly expandable	Immunosuppression required
Foetal Cardiomyocytes	Cardiomyocyte phenotype Electphysiologically compatible	Immunosuppression required, ethical debate Short survival and limited supply.
Resident cardiac system cells	Cardiac in origin, mechanically and electrophysiologically compatible source of cells for transplantation	In chronic phase of MI, the number of stem cells falls and the remaining cells have less regenerative potential
Skeletal Myoblasts (Satellite cells)	Lack of immunogenicity and autologous transplantation, high yield and fatigue-resistant, slow-twitch fibres	Electrophysiologically incompatible lack of gap junction-arrhythmogenic
Hematopoietic stem cells Bone marrow/Peripheral blood	Lack of immunogenicity and autologous transplantation-different lineage of cells	Quantum of cell population not adequate.
Endothelial Progenitor cells Bone marrow/Peripheral blood	Lack of immunogenicity and autologous transplantation-different lineage of cells	Need for expansion because of limited supply.
Mesenchymal Stem Cells Bone marrow stromal/Muscle, Skin and Adipose Tissue	Lack of immunogenicity, autologous transplantation, pluripotent and cryopreservable for future use.	Requires expansion.

19. PREBIOTICS AND PROBIOTICS

Probiotics are bacterial cultures or living microorganisms upon ingestion in certain quantity promote and enhance health benefits. *Prebiotics* are non-digestible food ingredients such as fructo-oligosaccharides (FOS), lactulose and insulin that beneficially affect the host by selectively stimulating growth and/or increasing the activity of a limited number of probiotic-like bacteria in the colon.

Species – Probiotics can be yeast, bacteria or moulds, bacterial species being predominant. Some of the species are –

1. *Lactic acid bacteria (LAB)* – Lactobacillus, Bifidobacterium, Streptococcus, Lactobacillus species help in production of enzymes to digest and metabolize proteins and carbohydrates. They aid in synthesis of vit. B and vit. K and facilitate breakdown of bile salts.
2. *Nonlactic acid producing bacterial species* – Bacillus propionibactreium. The benefits include metabolization of lactose and synthesization of vitamins, and help in reducing antibiotic associated diarrhoea and traveller's diarrhoea. They relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage, and may prevent or delay onset of cancer.
3. *Nonpathogenic yeasts* – Saccharomyces, Streptobacillus thermophilus and Lactobacillus bulgaricus metabolize lactose, improve lactose tolerance and antimicrobial activity.
4. *Nonsporeforming and non-flagellated rod or coccobacilli.*

Mechanism of action and indications for probiotics

1. *Immunity* – Regulatory T lymphocytes (Tregs) are thought to play a role in limiting inflammation in pathogenesis of some intestinal disorders.
2. *Probiotics and HIV* – It has been postulated that probiotic bacteria may slow down AIDS progression.
3. *Probiotics and cancer* – In addition to their conventional use as gut modulators, probiotics play a role in preventing colon cancer. Prebiotics also have the same effect, attributed to production of short chain fatty acids. Butyrate is one such protective agent.
4. *Prevention of Clostridium difficile diarrhoea.* Overall up to one quarter of patients treated with antibiotics develop diarrhoea caused by C difficile. Favourable results have been obtained with Lactobacillus rhamnosus GG or *Saccharomyces boulardii.*
5. *Functional GI disorders* in children and adults. Lactobacilli and bifidobacteria increase stool frequency and decrease consistency in constipation predominant IBS.
6. *Calcium absorption* – Probiotic given to individuals with lactose intolerance. The milk lactose is hydrolysed by probiotic strains and favours calcium absorption.

7. *Probiotics and oral health.* Probiotics have been successful for treating digestive related disorders. Some of the hypothetical mechanism of probiotic action in oral cavity are – Direct interaction in dental plaque, binding oral micro-organisms to proteins, or reduction of chemicals that inhibit oral bacteria. Indirect probiotic actions include modulating systemic immune function, effect on local immunity, regulation of mucosal permeability, action as antioxidants, production of antioxidants. Probiotic bifidobacterium reduce gingival and periodontal inflammation. Commonly used probiotics are sporolactobacilli, Saccharomyces boulardii and yogurt (L. bulgaricus), L. thermophilus, Bacillus mesentericus (genetically modified) as alternate to B complex.

20. CHEMICAL WARFARE

The acquisition of chemical weapons by a number of countries has increased the likelihood of their use by terrorists. Sulphur was used in the Iran-Iraq war. Some time back the release of ricin are examples of actual or potential chemical weapons. Nerve agents: The organophosphorous nerve agents are chemically related to organophosphorous insecticides. Two classes of nerve agents are recognised – G and V. Tabu Tabun, sarin and soman are the G agents. VX is the V agent. G agents are both dermal and respiratory, the V agents, unless aerosolized, are contact poisons.

Clinical features of toxicity: Systemic features may develop following ingestion and dermal and vapour exposure. Features follow most rapidly after inhalation.

Ocular exposure – Miosis, which may be painful and can last for several days. Ciliary spasm may impair accommodation.

Dermal exposure – Contact with liquid nerve agent may produce localized swelling and fasciculations which spread to involve whole muscle groups.

Inhalation – Chest tightness, rhinorrhoea and increased salivation. Ingestion of contaminated food or water may cause abdominal pain, nausea, vomiting and involuntary defecation.

Systemic features – Tremor, restlessness, ataxia and convulsions may follow. Bradycardia, tachycardia and hypotension may occur, dependent on whether muscarinic or nicotinic effects predominate.

Management – Urgent hospitalization. If rhinorrhoea or bronchorrhoea, atropine 2 mg in adults (20 mg/kg in children) IV q5-10 minutes till patient is atropinised. An oxime e.g. IV 30 mg/kg q4h in systemic features who require atropine or infusion of pralidoxime mesylate 8–10 mg/hr. Diazepam IV 10–20 mg (child 1–5 mg) for controlling agitation, fasciculation and convulsions.

Ricin is a globular glycoprotein and is readily produced as a by-product of castor oil production. Use of ricin to cause mass casualties would require either aerosolization by means of disposable device or its addition to food and beverages as a contaminant. By inhalation, (breathing in solid or liquid particles) and injection into muscle or a vein, the lethal dose is 5–10 mg/kg. Many of the features seen in poisoning are due to ricin-induced endothelial cell damage which leads to fluid and protein leakage and tissue oedema causing so-called 'vascular leak syndrome'.

Clinical features

Ricin is toxic via all routes, although features of poisoning varies with both route and dose.

Ingestion – Vomiting, abdominal pain and diarrhoea within a few hours. GI fluid and electrolyte loss may be complicated by haematemesis and melena and result in dehydration and hypovolemic shock. Liver and kidney damage may ensue. Death results from multi-organ failure.

Inhalation – Clinical features are those of an allergic response with conjunctivitis, rhinitis, urticaria and wheeze.

Parenteral administration. (a) In clinical trials of ricin as a chemotherapeutic agent, an IV dose of 0.3 mg/kg caused marked fatigue, myalgia, nausea and vomiting. (b) IM injection – Marked pain at site of injection followed by nausea, vomiting and fever over next 24 hours. GI hemorrhage is followed by hypovolemic shock and kidney failure.

Diagnosis - Detection of arthricin antibodies in individuals exposed to ricin who survive for 2–3 weeks. Antibodies will not be detected in those who die soon after exposure, in this situation, a ribosome inactivation test is more useful.

Management – is symptomatic and supportive for all routes of exposure.

Sulphur mustard is a colourless oily liquid. Its vapour has considerable penetrating ability, and it passes rapidly through clothing to affect the underlying skin and causes a chemical burn. The naturally moist areas of the body (e.g. genitalia, perineal region, groin, lower back, axillae) are often most severely affected. Erythema develops within a few hours and crops of blisters may appear at any time up to 2 weeks after exposure, necrosis is complete 4–6 days after exposure and separation of necrotic slough then begins, followed by scab formation.

Management – No specific treatment. IV fluids since substantial fluid loss may occur once blisters have formed. Bland lotions (e.g. calamine) for areas of erythema and minor blistering. Topical bacteriostatic agents (e.g. 1% silver sulphadiazine).

21. ANTIBACTERIAL CHEMOTHERAPY

Selection of an antibacterial drug – depends on – (a) Spectrum of activity. (b) Its distribution to the site of infection. (c) Clinical proof of efficiency in a given situation.

Indications for combined antibacterial therapy

1. To achieve a synergistic effect, e.g. penicillin and gentamicin for *Strep. faecalis* endocarditis.
2. To reduce likelihood of emergence of drug resistance e.g. treatment of tuberculosis.
3. To treat mixed infections, e.g. both aerobic and anaerobic infections in GI or female genital tract sepsis.
4. To treat severe infection at an initial stage when the causative agent is not known.

Antibiotic resistance – The term 'antibiotic resistance' implies that a particular antibiotic is ineffective in a clinical inference. This may be because the organism is inherently resistant to the antibiotic or because it is inaccessible. *In vitro* resistance is defined by measuring the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of the antibiotic against an organism using appropriate controls to define the cut-off points between 'resistant', 'intermediate' and 'sensitive'. Low MIC and high MBC imply that an antibiotic is bacteriostatic; that is it inhibits the growth of an organism but is unable to kill it. Even with bactericidal antibiotics, killing *in vivo* normally requires an intact immune system.

Mechanisms of resistance. Resistance may be inherent (e.g. vancomycin against Gram-negative organisms, nitrofurantoin against Proteus spp.) or may be acquired via genetic elements encoding three fundamental mechanisms:

1. **Antibiotic-inactivating enzymes** – may be produced in vast excess, surrounding the organism (e.g. β-lactamase from *Staph. aureus*, or in limited amounts in periplasmic space of Gram-negatives. The effect *in vivo* is similar, but the latter organisms may appear sensitive *in vitro*.
2. **Target site change** may be a structural alteration preventing binding of an antibiotic, or a mechanism whereby the metabolic pathways that is normally inhibited is bypassed by an alternative one. This is seen in sulphonamide resistance and in methicillin-resistant *Staph*. aureus. Important target site changes include topoisomerases II and IV (quinolones), B subunit of DNA-dependent RNA polymerase (rifamycins) and methylation of 23S target (macrolides).
3. **Exclusion of antibiotic** from the target site. Porins are protein structures embedded in the outer bilipid membrane of Gram-negative organisms. They control what passes into and out of the cell on basis of molecular size and charge. Mutations of the genetic elements encoding porins (permeability mutations) may exclude one antibiotic or more commonly multiple antibiotics *P. aeruginosa* has two outer lipid membranes, produces β-lactamases constitutively, and therefore tends to be more resistant than coliforms. Alternatively, organisms may actively excrete antibiotics, notably tetracyclines, macrolides and quinolones.

Table 37: Main classes of antibiotics and antibacterial drugs

Class, action	*Indications*	*Adverse effects*
β-lactams		
Inhibit bacterial cell formation		
Bacteriostatic		
Meropenem Ertapenem		
Penicillins	**Clinical Use**	
Classifications 1. Bronchospasm. susceptible strains of enterococci penicillin	Penicillin G for infections due to Step. 1. Aminocillins for upper and lower resp. Tract infections bacterial gastroenteritis bacterial endocarditis, meningitis, UTIs cause by susceptible (i.e. non-β-lactamase producing organisms) and tr. of ulcers and gastric infections cause by H. pylori	1. *Hypersensitivity reactions* – Rash, fever, Natural penicillins, pyogenes, penicillin-Vasculitis, serum sickness, exfoliation, Stevens Johnson-penicillin G and Strep-pneumonia and syndrome and anaphylaxis. 2. *Other* – Diarrhoea with oral penicillin, particularly amoxicillin. Interstitial nephritis and encephalopathy with high doses in patients with renal failure. Hypersensitivity?

Contd...

Contd...

Class, action	*Indications*	*Adverse effects*
2. Penicillinase-resistant encephalopathy penicillins, methicillin, nafcillin and isoxazolyl penicillins		
3. Aminopenicillins, ampicillin, amoxicillin		
4. Carboxypenicillins, carbenicillin and ticarcillin		
5. AcyH ureidopenicillins, azlocillin, mezlocillin and piperacillin		
Action		
Inhibition of bacterial cell wall synthesis **β-lactam and β-lactamase inhibitors combinations** Action-Inhibition of Class C and class β-lactamases Drugs: Clavulanic acid, sulbactam and tazobactam		
Carbapenems		
Action, Bactericidal Inhibit cell wall synthesis		
Imipenem Meropenem Ertapenem Doripenen	Most anaerobic and aerobic pathogens (except xanthomonas maltophilia and some strains of P. cepacia). Largely used for serious intra-abdominal infections.	Diarrhoea, nausea, vomiting, abdominal pain Contraindicated in patients who are hypersensitive to β-lactams and those with CNS disease, especially in presence of renal failure because of increased risk of seizures.
Cephalosporins		
First generation Oral: • Cephalexin • Cephradine • Cefadroxil • Cefditoren	Mainly active against Gram-positive bacteria. Used only if intolerance or resistance to other agents	1. *Hypersensitivity reactions* as in case of penicillins. 2. *Renal tubular necrosis* – in case of high doses of cephalothin (less likely with third generation group) 3. *Bleeding.*
Parenteral: • Cephalothin • Cephazolin		
Second generation		
Oral: • Cefaclor • Cefuroxime axetil • Cefetamet pivoxil	Cefuroxime – Active against Staphylo., Strepto., Gram-ve bacteria, e.g. E. coli, Proteus spp., H. Influenzae, N. Gonorrhoea and some Klebsiella spp.	
Parenteral: • Cefuroxime • Cefamandole • Cefoxitin • Cefepime • Aztreonam		
Third generation		
Oral: • Cefixime • Cefpodoxime proxetil • Ceftibutin • Cefdinir • Cefditoren	Aerobic Gram-ve and Gram +ve bacteria, many anaerobic bacteria, including B. fragilis.	

Contd...

Contd...

Class, action	*Indications*	*Adverse effects*
Parenteral: • Cefotaxime • Cefotaxime • Cefoperazone • Ceftazidime • Ceftriaxone • Cefsulodin • Cefodizime	Activity against many Gram-ve bacilli, comparable to aminoglycosides Similar to cefotaxime Most Gram-ve bacteria and P. aeruginosa All forms of gonorrhoea, childhood meningitis P. aeruginosa Most Gram-ve bacilli and Streptococci.	GI side effects
Fourth generation Cefepime Cefpirome	P. aeruginosa and enterococci Also plague and tularemia	
Oxazolidinones Inhibit neuritis protein synthesis Linezolid	Gram +ve bacteria including methicillinresistant Staph. aureus. Vancomycin-resistant enterococci and penicillin resistant S. pneumonia.	Reversible bone marrow suppression, optic neuritis lactic acidosis, headache, hypertension
Quinolones Inhibit bacterial DNA synthesis Bactericidal		
Nalidixic acid Oxolinic acid Fleroxacin Gemifloxacin	Urinary tract infections	Headache, nausea, vomiting, diarrhoea
Ciprofloxacin Pefloxacin Ofloxacin Norfloxacin Levofloxacin Lomefloxacin Gatifloxacin Sitafloxacin Moxifloxacin Plurifloxacin Biofloxacin	Active against aerobic gram-negative bacilli, particularly Enterobacteriaceae, M. catarrhalis, Haemophilus and Neisseria Ciprofloxacin and levofloxacin and gemifloxacin are active against M. tuberculosis, M. fortuitum, M. kansasii and against genital pathogens like C. trachomatis, U. urealyticum and M. hominis **Clinical Uses** UTI, resp. tract, infections, GI bone and joint and skin and tissue infections	Occasional photosensitivity, GI intolerance and CNS toxicity.
Aminoglycosides Inhibit bacterial protein synthesis Bacteriostatic Streptomycin Gentamicin Kanamycin Tobramycin Netilmicin Amikacin	Second line treatment for T.B. Gram-neg. bacilli including P. aeruginosa (resistant to amikacin), Strep. pneumoniae, anaerobic bacteria. Often combined with penicillin or cephalosporin for life-threatening infections and metronidazole if anaerobic infection is likely.	1. *Ototoxicity and nephrotoxicity.* 2. *Other side effects* – Neuromuscular blockade (hence not to be prescribed in myasthenia gravis), very occasionally bleeding. 3. *Effects in foetus* – May cause VIIIth nerve damage (hence to be avoided in pregnancy).
Neomycin	Used orally for hepatic encephalopathy	
Macrolides		
Interfere with bacterial protein synthesis Bacteriostatic. Lack activity against most methicillin resistant staphylococci Erythromycin Clarithromycin	Staphylo and Streptococcal infections. As effective as tetracycline for M. pneumoniae and Coxiella burnetti infections. Drug of choice for Legionnaire's disease, and is active against all sero-groups of Legionella pneumophilia and other Legionella-like organisms. More active than erythromycin – M. tuberculosis and M. avium intracellulare, Legionella pneumophilia and other atypical resp. pathogens.	*Cholestatic hepatitis* – The jaundice is accompanied by elevated aminotransferase enzymes, fever, leucocytosis and eosinophilia

Contd...

Contd...

Class, action	*Indications*	*Adverse effects*
Azithromycin	Atypical mycobacteria, Chlamydiae trachomatis. Toxoplasmosis (in patients with HIV).	
Tetracyclines		
Interfere with bacterial protein synthesis Bacteriostatic Oxytetracycline Doxycycline Minocycline	Brucellosis, cholera, chlamydiae and mycoplasma infections. Ricketssial and Coxiella infections.	1. *GI side effects* – GI irritation and rarely oesophageal ulceration. 2. *Renal side effects* – Aggravation of pre-existing renal failure (not doxycycline and minocycline). 3. *Tooth pigmentation and dental enamel hypoplasia* in infants and children under 8 years of age.
Chloramphenicol	H. influenzae meningitis and epiglottitis due to ampicillin-resistant strains or drug sensitivity to cephalosporin. Bacterial meningitis. Typhoid fever and anaerobic	1. Aplastic anemia. 2. Suppression of bone marrow – This is dose-dependent. 3. Grey baby syndrome – of cardiovascular collapse sepsis may develop in neonates
Lacosamide antibiotics		
Lincomycin Clindamycin Action: have same or overlapping 50S ribosomal binding sites as for macrolides	Staphylo, pneumo, S. pyogenes Streptococci Unidamycin has activity against T. gondii, P. jiroveci and P. falciparum	Diarrhoea, kidney or liver impairment
Glycopeptides		
Inhibit cell wall synthesis in dividing bacteria vancomycin	Gram-positive organisms Enterococcus faecalis including all strains of Streptococci	Infusion related (redman syndrome) Pseudomembranous colitis. Deafness.
Lipopeptides		
Daptomycin Antimicrobial activity	Gram-positive pathogens including isolates resistant to methicillin, vancomycin	Myopathy
Polymixin and Colistin Penetrate into cell membranes and disrupt the membranes	Post-antibiotic effect (PAE) for pseudomonas, Gram-negative aerobic bacilli Colistin sulphate po for intestinal decontamination Colistimethate by parenteral, inhalational and intraventricular route to treat infections caused by MDR gram-negative bacilli	Dose-related nephrotoxicity and neurotoxicity
Sulphonamides and Trimethoprim		
Interfere with folate synthesis in bacteria		
Sulphonamides		
Sulphadimidine Sulphathiazole Sulphamethizole	Combination therapy for urinary and resp. tract infections Co-trimoxazole drug of choice for Pneumocystis carinii pneumonia and long-term prevention of this infection in patients infected with HIV.	Stevens-Johnson syn., hemolytic anemia, marrow aplasia, agranulocytosis, thrombocytopenia, hepatotoxicity.
Trimethoprim Trimethoprim Tetroxoprim		
Fusidic acid	Staphylococcal infections such as osteomyelitis and pneumonia usually combined with anti-staphylo. penicillin or erythromycin.	Generally well tolerated. Nausea, hepatotoxicity.
Nitroimidazoles		

Contd...

Contd...

Class, action	*Indications*	*Adverse effects*
Metronidazole Tinidazole Secnidazole	Amoebiasis. Trichomoniasis. Anaerobic infections (e.g. intra-abdominal and female genital tract infections, brain abscesses).	Peripheral neuropathy (dose dependent).
Rifampicin	Tuberculosis. Staph. epidermis infections (combined with flucloxacillin to reduce risk of drug resistance). Legionnaire's disease. Chemoprophylaxis of meningococcal and H. *influenzae* meningitis.	1. Jaundice. Incidence of severe hepatic problems increases when the drug is used in combination with isoniazid. 2. Other side-effects – Thrombo-cytopenia, eosinophilia, transient neutropenia and hemolytic anemia.

22. SOME COMMON SYMPTOMS AND SIGNS

Absent ankle jerks with extensor plantar

1. Subacute combined degeneration.
2. Friedreich's ataxia.
3. Taboparesis.
4. Motor neuron disease.
5. Diabetic amyotrophy.
6. Combined lumbar and cervical spondylosis.
7. Conus medullaris lesion.
8. Meningeal carcinomatosis.
9. Spinal shock.

ACANTHOSIS NIGRICANS

Brown to black hyperpigmented lesions velvety in structure, sites in such as creases of axillae, neck, groins.

A. **Benign**
   1. Hereditary benign (AD)
   2. Benign acanthosis nigricans

   Endocrine: Acromegaly, Cushing's disease, Addison's disease, insulin-resistant DM, hypothyroidism, Bloom's syndrome, Crouzon's syndrome, hyperandrogenic states

   3. Pseudo-AN: Complication of obesity (more common in individuals with dark complexion)

   Drug-induced: Nicotinic acid, stilboestrol, oral contraceptives, folic acid antagonists (triazine), methyltestosterone.

B. **Malignant AN:** Paraneoplastic, usually associated with adenocarcinoma of GI tract or genitourinary tract, rarely lymphoma.

ACUTE ABDOMINAL PAIN

All age groups

- Appendicitis
- Perforated peptic ulcer
- Acute cholecystitis
- Renal colic
- Factitious pain (Munchausen syndrome)
- Diverticular disease
- Acute intestinal obstruction
- Nonspecific abdominal pain
- Dyspepsia

Elderly

- Urinary tract infection
- Vascular (myocardial infarction, aortic aneurysm, mesenteric ischemia)
- Medical causes, e.g. pneumonia

Children

- Intussusception
- Hernia
- UTI
- URTI

Women

- Salpingitis
- Ovarian cyst
- UTI
- Ectopic pregnancy

ACUTE FLACCID PARALYSIS

1. Poliomyelitis
2. Diplegia (cerebral palsy)
3. Guillain-Barre syndrome
4. Acute motor neuropathy
5. Transverse myelitis
6. Injury to nerves, traumatic neuritis
7. Japanese encephalitis virus
8. Hypokalaemia in malnourished children
9. Hopkins syndrome. Poliomyelitis - like illness with a flaccid paralysis of an extremity during the recovery stage of an asthmatic attack.
10. Miscellaneous
    a. Viral myositis
    b. Osteoarticular trauma
    c. Dystrophies

d. Acute cerebellitis
e. Retroperitoneal tumors
f. Upper motor neuron syndrome
g. Myopathies
h. Non-poliovirus enterovirus-induced paralysis

ANGULAR CHEILITIS

1. Riboflavin deficiency.
2. Iron deficiency anaemia.
3. Excessive intake of tobacco, betel nut, alcohol.
4. Herpes labialis at angles of mouth.
5. Ill-fitting dentures.

ANOREXIA

1. *Infections and chronic diseases* – Acute febrile illness, chronic infections like tuberculosis. Hepatic, renal, cardiac, haemopoietic and adrenal disease.
2. *Lessened metabolic function* – Addison's disease, hypothyroidism, Simmond's disease.
3. *Local causes due to decreased hydrochloric acid secretion* – Carcinoma of stomach, chronic gastritis, pernicious anaemia, etc.
4. *Psychic causes* – Mental worry, fear, anorexia nervosa.
5. *Deficiency of vitamins* – particularly B complex.
6. *Physiological anorexia* – Inactive life, irregular eating and drinking, excess of carbohydrate food in between meals.

Management – (a) If symptomatic, the disease must be treated. Gastric lavage if there is pathological retention of food in the stomach. (b) Diet – Appetising food. No sweets between meals. No hurry. (c) Exercise and fresh air. (d) Avoidance of excessive smoking and alcohol. (e) Appetisers – Cyproheptadine hydrochloride – in dose of 2–4 mg. according to age as tablets or syrup b.d. Contraindicated in glaucoma and urinary retention. Produces drowsiness, or rarely agitation and confusion. (f) Vitamin B_{12}' multivitamins. (g) Anabolic steroid – Norethandrolone 50 mg. daily by mouth or 25 mg. I.M. once a week.

ASCENDING PARALYSIS (ACUTE)

1. Poliomyelitis
2. Acute myasthenia gravis
3. Snake bite
4. Botulism
5. Tick paralysis
6. Shellfish poisoning

ATAXIA

1. **Sensory ataxia** –
   a. *Peripheral sensory nerves* – Peripheral neuritis.
   b. *Posterior roots* – Tabes, syphilitic pachymeningitis.
   c. *Posterior columns* – Multiple sclerosis, spinal tumours, syringomyelia, subacute combined degeneration.
   d. *Post-central convolution* – Disorders of parietal lobe.
2. **Cerebellar ataxia** –
   a. *Cerebellum* – Cerebellar tumour or abscess, cerebellar artery thrombosis, progressive cerebellar degeneration.
   b. *Cerebellar pathways* – Cerebellopontine angle tumour, encephalitis, Friedreich's ataxia.
3. **Labyrinthine ataxia** – Acute labyrinthitis, haemorrhage into internal ear, acute lesions of vestibular nucleus in medulla, attacks of vertigo of Meniere's disease.

BACKACHE

1. ***Diseases of vertebral column*** – Pott's disease, tumour, diseased intervertebral disc, sacroiliac arthritis, osteitis fibrocystica, osteitis deformans, osteomalacia, osteoporosis of various types. Congenital malformation, e.g. sacralization of 5th lumbar vertebra. Spondyloarthritis or spondyloarthrosis, multiple myeloma, malignant deposits.
2. ***Disease of spinal cord and meninges*** – Trauma, infection, neoplasm.
3. ***Soft tissue involvement*** – Fibrositis (lumbago); acute traumatic injury causing contusion, haemorrhage, rupture of muscle fibres, fascia or ligaments. Acute infections such as influenza, exanthemas, dengue, brucellosis, chikungunya.
4. ***Referred pain*** – (a) Pancreas – tumour, cyst or sometimes even chronic pancreatitis. (b) Lymph nodes – lymphosarcoma, Hodgkin's disease, lymphatic leukaemia or cancerous metastases. (c) Retroperitoneal hematoma. (d) Aneurysm of abdominal aorta. (e) Kidney disease – Calculi, tumours, tuberculosis, polycystic kidneys, hydro-or pyonephrosis, pyelonephritis, perinephric abscess. (f) Disease of female genital organs (gynaecologic backache). (g) Disease of prostate. (h) Cancer of rectum.
5. ***Faulty body posture***.
6. ***Depression.***

BASILAR INVAGINATION

1. ***Delayed or defective cranial ossification*** – Osteogenesis imperfecta, achondroplasia, cleidocranial dysplasia, cranial thinning due to hydrocephalus.
2. ***Klippel-Feil syndrome*** – Fusion of bodies of some cervical vertebrae.
3. ***Generalized bone disease*** – Osteomalacia, rickets, Paget's disease, fibrous dysplasia.

CAFE-AU-LAIT SPOTS

(Five or more with at least one with long axis more than 1 cm. to be significant).

1. Neurofibromatosis (von Recklinghausen's disease).
2. Albright's disease (Polyostotic fibrous dysplasia).
3. Watson's syndrome (Pulmonic stenosis).
4. Normal individuals (about 10%).

Calf muscle enlargement or hypertrophy

1. Hereditary – Duchenne or Becker myopathy, Charcot-Marie- Tooth disease.
2. Myositis ossificans.
3. Parasitic – Trichinosis, cysticercosis.
4. Endocrine – Acromegaly, hypothyroidism.
5. Amyloidosis.
6. Traumatic.

CANNON 'A' WAVES

Isolated – Ventricular ectopics.

Regular – (a) At normal heart rate: Nodal rhythm, sinus rhythm with prolonged PR. (b) At rapid rate: Isorhythmic AV dissociation, ventricular tachycardia with 1:1 retrograde conduction.

Irregular – (a) Slow rate: Complete heart block. (b) Fast rate: Ventricular paroxysmal tachycardia.

CAROTENEMIA

1. Excessive intake of carrots
2. Hypothyroidism
3. Diabetes mellitus
4. β-carotene therapy for erythropoietic porphyria
5. Anorexia nervosa.

CARPAL TUNNEL SYNDROME

1. Idiopathic
2. Compression of median nerve by fracture, oedema or tenosynovitis
3. Rheumatoid arthritis
4. Osteoarthritis
5. Myxoedema
6. Acromegaly
7. Palindromic rheumatism
8. Primary amyloid
9. Pregnancy

CHARCOT FOOT

- Diabetes mellitus (major cause)
- Leprosy
- Tabes dorsalis
- Spinal cord tumour
- Charcot-Marie-Tooth disease
- Drugs: Steroids, indomethacin, phenylbutazone, vincristine
- Alcoholism
- Cerebral palsy
- Hereditary insensitivity to pain
- Myelodysplasia
- Poliomyelitis
- Syringomyelia
- Tertiary syphilis

CHYLURIA

1. Primary or idiopathic
2. Secondary –
   a. *Parasitic* – Filaria, ascaris, trichomonas, echinococcus, tinea and H. nana infestation, Ankylostoma, malaria.
   b. *Non-parasitic* – Obstruction or traumatic injury of thoracic duct, thrombosis of left subclavian vein, neoplasms, retroperitoneal fibrosis, pregnancy. Congenital lymphangiectasia involving urinary tract.

CLUBBING OF FINGERS

1. **Symmetrical** –
   a. ACQUIRED – (i) *Pulmonary* – Pleural, mediastinal or pulmonary disease due to compression, infection, foreign body or neoplasm. (ii) *Cardiac* – Cyanotic congenital heart disease, SBE, occasionally congestive heart failure. (iii) *Liver disease* – Cholangiolitic cirrhosis. (iv) *Gastro-intestinal* – ulcerative colitis, chronic dysentery, idiopathic steatorrhoea. (v) *Miscellaneous* – Myxoedema, particularly iatrogenic; exophthalmic ophthalmoplegia.
   b. Hereditary – May be familial condition and is often asymmetrical.

c. IDIOPATHIC – Cases without family history or recognizable underlying disease.

2. **Unilateral or unidigital** –
   - Aneurysm of aorta or its branches
   - Brachial A-V fistula
   - Subluxation of the shoulder
   - Pancoast tumour
   - Erythromelalgia
   - Local trauma
   - Felon (suppurative nail pulp infection)
   - Tophaceous gout
   - Sarcoidosis

CLAW HAND

1. Leprosy
2. Progressive muscular atrophy, amyotrophic lateral sclerosis
3. Median and ulnar nerve injury
4. Brachial plexus injury
5. Cervical rib or cervical pachymeningitis
6. Syringomyelia.
7. Acute poliomyelitis (rare).

COMA OF VARYING DEPTH

1. On and off gastrointestinal absorption, e.g. with meprobamate which forms concretions in the gut.
2. Enterohepatic circulation.
3. Secondary effect of hypoxia on consciousness.
4. Brief action of narcotic antagonists versus long action of opiates.
5. Brief action of glucose versus long-acting hypoglycaemic agents.
6. Subdural hematoma.

COUGH (PERSISTENT)

1. *Infections* –
   a. Viral bronchial infection.
   b. Nasal and sinus infection.
   c. Chronic bronchitis.
   d. Pulmonary TB.
   e. Bronchiectasis.
2. *Bronchial asthma.*
3. *Bronchial carcinoma.*
4. *Pulmonary fibrosis.*
5. *Repeated bronchial aspiration* –
   a. Oesophageal disorders. GERD
   b. Neurological disease affecting swallowing.
6. *Drug-induced cough* – ACE inhibitors.
7. *Psychogenic.*

CRANIAL BRUITS (IN ADULTS)

1. Transmitted from aortic or carotid artery stenosis.
2. Carotid-cavernous sinus fistula.
3. Arteriovenous malformations of cerebrum.
4. Angiomatous conditions in the orbit.
5. Vascular intracranial tumours, e.g. some meningiomas.
6. Glomus jugulare tumours.

CYANOSIS

1. **Central cyanosis** – is due to diminished arterial oxygen saturation. It is visible in the skin (nose, cheeks and fingers), and in warm areas, viz. those richly supplied with blood vessels (tongue, lips, conjunctivae). Central cyanosis, if severe and of long duration is associated with clubbing of fingers, and polycythemia.

Causes

a. *Veno-arterial shunts* – e.g. Fallot's tetralogy, Eisenmenger's syndrome.

b *Impaired arterial oxygenation* – (i) Impaired diffusion of oxygen due to pulmonary disease, e.g. consolidation, atelectasis, emphysema, fibrosis. (ii) A low partial pressure of the alveolar oxygen as occurs at high altitudes.

2. **Peripheral cyanosis** – is due to a peripheral mechanism, i.e. an increased arteriovenous oxygen difference. It is visible only in the skin (nose, cheeks, fingers) and not in warm areas (tongue, lips, conjunctivae). Clubbing of the fingers and polycythemia do not occur.

Causes

a. Slowing of circulation due to cold, or excess vasomotor stimulation.

b. Oxygen deficiency with carbon dioxide accumulation – obstruction to trachea, venous congestion.

c. Increased venous pressure producing stagnation and cyanosis – right sided heart failure, tricuspid stenosis, acute or chronic constrictive pericarditis, venous thrombosis.

d. Shock because of vasomotor collapse and stagnation of blood.

3. **Mixed cyanosis** – due to combination of both factors, e.g. in cor pulmonale due to pulmonary emphysema.

DEHYDRATION

1. *Failure of fluid intake* – Unavailable, nausea, psychic disorder.
2. *Failure of absorption* – Diarrhoea, intestinal disorders.
3. *Loss from gastrointestinal tract* – Vomiting and diarrhoea.
4. *Excessive renal loss* – (a) Due to renal factors, e.g. failure of renal absorption. (b) Due to pre-renal factors – Disturbed body fluid chemistry, e.g. diuretics, cathartics.
5. *Excessive perspiration.*
6. *Loss from burns, wounds, etc.*

DELAYED PUBERTY (BOTH SEXES)

1. *Physiological* or constitutional.
2. *Non-endocrine diseases* – Asthma, steatorrhoea, chronic liver disease, helminthic infestation, haemoglobinopathies, chronic malaria, malnutrition.
3. *Chromosomal and endocrine disorders* – Turner's syndrome (in girls), Klinefelter's syndrome (in boys).
4. *Juvenile myxoedema.*
5. *Cushing's syndrome.*
6. *Pituitary failure* – Chromophobe adenoma or craniopharyngioma.

DIPLOPIA

1. *Monocular* – In disease of the eye and hysteria.
2. *Temporary* – Myasthenia gravis, vascular disease affecting brainstem, migraine, post-concussion, acute alcoholism, fever, toxic states. States of nervous tension.
3. *Long-lasting (usually)* – Encephalitis, meningitis, head injury, tumours, subarachnoid haemorrhage, hypertensive encephalopathy, Wernicke's encephalopathy, abscess of brain or cerebellum, cavernous sinus thrombosis, botulism.
4. *Gradually worsening diplopia* – Compression from aneurysm, pituitary tumour, meningovascular syphilis, tuberculous meningitis, post-nasal carcinoma or tumour at base of skull.
5. *Very slowly progressive* – Ocular myopathy, thyrotoxic ophthalmoplegia. Lesions in the orbit such as arteriovenous fistula in cavernous sinus, orbital tumour.

DYSPNOEA

A feeling of laboured, or unnaturally difficult breathing.

1. *Mechanical impairment of ventilation* – (a) Muscular weakness as in poliomyelitis or myasthenia. (b) Skeletal fixation, as from marked chest wall deformity or spondylitis. (c) Hydrothorax, pneumothorax. (d) Ascites or marked abdominal distension due to other causes. (e) Tracheal or bronchial obstruction.
2. *Impairment of pulmonary distensibility* – (a) Pulmonary congestion. (b) Pulmonary fibrosis.
3. *Pulmonary insufficiency* (inadequately functioning alveolar tissue) – (a) Emphysema. (b) Extensive inflammatory disease of pulmonary parenchyma.
4. *Inadequate delivery of oxygen to tissues* – (a) High altitude. (b) Anaemia. (c) Cardiac failure.
5. *Hyperventilation of central type, as from acidosis* – (a) Nephritic. (b) Diabetic.
6. *Psychic.*

Time course for onset of dyspnoea –

Seconds –

- Pneumothorax
- Pulmonary oedema due to arrhythmias
- Pulmonary embolism
- Inhalation of foreign body

Hours –

- Asthma
- Left heart failure
- Pneumonia
- Laryngeal oedema
- Hemorrhage
- Hypersensitive pneumonitis

Days –

- Pneumonia
- ARDS
- Left heart failure

Weeks to months –

- Pleural effusion
- Anemia
- Muscle weakness
- Tumours
- Pulmonary fibrosis
- Chronic airways obstruction
- Thyrotoxicosis
- Chest wall disorders

ENLARGED GREAT AURICULAR NERVE

1. Leprosy
2. Amyloidosis

3. Neurofibromatosis
4. Hypertrophic peripheral neuropathy
5. Refsum's disease

EPISTAXIS

1. **Local causes –**
   a. Spontaneous.
   b. Trauma to nose, base of skull, or from foreign body.
   c. Nasal disease – acute ethmoidal sinusitis, nasal diphtheria, rhinitis sicca, tumours of nasal and paranasal sinuses, angiomas.
2. **Systemic disease –**
   a. *Infections* – Influenza, measles, typhoid fever, malaria, viral infections of upper respiratory tract, viral haemorrhagic fever including dengue fever.
   b. *Arterial hypertension.*
   c. *Venous hypertension* – Whooping cough, chronic bronchitis, emphysema.
   d. *Connective tissue disorders* – Ehlers-Danlos syndrome, pseudoxanthoma elasticum.
   e. *Bleeding disorders* – Haemophilia, leukaemia, thrombocytopenia, anticoagulants.
3. **Miscellaneous** –
   a. Mountain or air sickness.
   b. Hypersplenism.
   c. Hereditary haemorrhagic telangiectasia.

ERYTHEMA NODOSUM

1. Rheumatic fever.
2. Infections – Streptococcal, tuberculosis (especially primary), toxoplasmosis, histoplasmosis, brucellosis, leprosy, blastomycosis, coccidioidomycosis, lymphogranuloma inguinale, psittacosis, rickettsial infection, cat scratch fever, trichophytosis.
3. Inflammatory bowel disease.
4. Drugs – Sulphonamides, oral contraceptives, barbiturates.
5. Sarcoidosis.
6. Immunological – Behcet's disease.

ERYTHROMELALGIA

A syndrome of red congestion and burning pain in hands and feet.

1. Erythromelalgia associated with thrombocythemia.
2. Primary erythromelalgia – begins in childhood or adolescence as bilateral symmetrical burning distress in feet, ankle and legs, aggravated by warmth and exercise.
3. Secondary erythromelalgia – in association with gout, SLE, RA, cryoglobulinaemia, thromboangiitis obliterans, polyarteritis nodosa, arteriosclerosis, diabetes mellitus, neurological conditions, vascular diseases and secondary to vasoactive drugs.

EXOPHTHALMOS (PROPTOSIS)

Unilateral –

1. *Dysthyroid.*
2. *Orbital neoplasms* – Optic nerve glioma, retinoblastoma, metastases, etc.
3. *Vascular* – A-V malformation, hematoma, carotid-cavernous fistula.
4. *Obstructive lesions* – (a) *Intracranial* – Meningioma, glioma, cavernous sinus thrombosis, infraclinoid aneurysm. (b) *Sinus/bone lesion* – Fibrous dysplasia, neoplasm (carcinoma, osteoma, dermoid), mucocoele (extending from frontal sinus), craniostenosis.

Bilateral –

1. Graves' disease.
2. Cavernous sinus thrombosis.
3. Chronic emphysema (Frog's eyes).
4. Myasthenia gravis.
5. Paget's disease of bone.
6. Orbital myositis.
7. Uraemia.
8. Alcoholism.
9. Malignant hypertension.
10. SVC obstruction.
11. Carcinomatosis.
12. Craniostenosis

FACIAL ERUPTIONS

1. Vasomotor instability – provoked by stimuli such as warmth, hot drinks, alcohol, sun, emotion, pregnancy, odours and fumes.
2. Menopausal flushing.
3. Facial telangiectasia.
4. Carcinoid syndrome.
5. Superior vena caval syndrome.
6. Rosacea.
7. Corticosteroid red face.
8. Perioral dermatitis – Groups of pimples around the mouth.
9. Seborrhoeic dermatitis.
10. Contact dermatitis.

11. Atopic dermatitis (eczema).
12. Psoriasis.
13. Light sensitivity.
14. Lupus erythematosus – (a) Discoid: Slightly, bluish-red, thickened patches on cheeks, nose or chin. (b) SLE – Butterfly eruption.
15. Erysipelas.
16. Port wine stain.

FATIGUE (TIREDNESS)

1. *Psychogenic* – Neurosis or depression.
2. *Organic causes* – (a) *Cardiac* – Congestive failure, atrial fibrillation, hypertension, congenital heart disease. (b) *Respiratory* – Obstructive airways disease. (c) *Neurological* – Myasthenia gravis, myopathy. (d) Hemopoietic – Anaemia, lymphoma. (e) Endocrine – Hypothyroidism, hyperthyroidism, Cushing's syndrome, hypopituitarism, chronic adrenal insufficiency, diabetes mellitus (uncontrolled).
3. *Chronic infection* – Malaria, brucellosis, pulmonary tuberculosis.
4. *Iatrogenic causes* – e.g. diuretics, hypotensive drugs.
5. *Prolonged inactivity.*

FLATULENCE

1. *Aerophagia* (air swallowing) – (a) Faulty dietary habits – Eating fast, excessive consumption of carbonated drinks, or of tobacco, spicy foods, betel leaves, candies. (b) Psychological – Anxiety, grief, nervous tension. (c) Hypersalivation – Gastritis, peptic ulcer. (d) Reflex – Angina pectoris, chronic cholecystitis, hiatus hernia. (e) Dryness of mouth – Dehydration, mouth breathing, anticholinergics.
2. *GI fermentation* – (a) Faulty diet containing inadequately cooked starch or cellulose. (b) Gastrointestinal stasis – Constipation, after vagotomy, intestinal strictures. (c) Intestinal hurry – Diarrhoea, cathartics. (d) Deficiency of digestive enzymes. (e) Malabsorption states. (f) Abnormal bacterial flora, e.g. use of broad spectrum antibiotics.
3. *Mechanical obstruction* – to passage of food and gas – Cascade stomach, intestinal obstruction.

Management

Gastric flatulence – (a) Treatment of aerophagia. (b) Avoid gulping down food, much talking during meals. (c) Chew food thoroughly and eat slowly. (d) Antacid-antiflatulent tablets or liquid after meals. (e) Carminative preparation.

Intestinal flatulence – (a) Avoid gas forming foods such as cabbage, cauliflower, cucumber, beans, peas, onions, raisins, nuts, apples. (b) Rule out amoebic infection. (c) Minimum consumption of sugar if associated diarrhoea. (d) Enzyme digestants after meals.

FOOT DROP (UNILATERAL)

1. *Pyramidal lesion* – affecting lower limb, e.g. hemiplegia, multiple sclerosis.
2. *Lateral peroneal nerve* – palsy.
3. *L5 root lesion* – from prolapsed disc.
4. *Charcot-Marie - Tooth disease.*

GENITAL AND ORAL ULCERATION

1. Reiter's syndrome.
2. Crohn's disease.
3. Pemphigus.
4. Erythema multiforme.
5. Syphilis.
6. Herpes simplex.
7. Behcet's syndrome.

GLOBUS SENSATION

1. Gastrooesophageal reflux disease
2. Anxiety disorder
3. Early hypopharyngeal cancer
4. Goitre

GOITRE

The term goitre is used to describe an enlargement of the thyroid.

1. *Iodine deficiency.*
2. *Idiopathic.*
3. *Physiological* – Puberty, pregnancy.
4. *Graves' disease.*
5. *Goitrogens* – Antithyroid drugs, iodine containing medicine, aminoglutethimide, lithium. Foods – soyabean, cassava.
6. *Thyroiditis* – Hashimoto's, acute or subacute (de Quervain's), Riedel's septic.
7. *Dyshormonogenesis* – Iodide trapping defect, organification defect (including Pendred's syndrome), impaired thyroglobulin synthesis, coupling or dehalogenase defects, end-organ resistance to thyroid hormone.
8. *Tumours* – Adenoma, carcinoma, lymphoma.
9. *Others* – Sarcoidosis, syphilis.

GUM BLEEDING

1. Gingivitis and gingivostomatitis.
2. Bleeding disorders – Thrombocytopenia, haemophilia, leukaemia, anticoagulants.
3. Abnormalities of vessel wall – Scurvy, Henoch-Schonlein purpura, dysproteinemia, e.g. multiple myeloma.
4. Connective tissue disorders (hereditary) – Ehlers-Danlos syndrome, pseudoxanthoma elasticum.

GYNECOMASTIA

1. **Physiological** –
   a. Neonatal.
   b. Pubertal.
   c. Senile.
2. **Pathological** –
   a. *Increased oestrogen production* –Cirrhosis of liver, thyrotoxicosis, Leydig cell tumours and adrenal carcinomas. Carcinoma of bronchus and other tumours (from secretion of HCG).
   b. *Decreased androgen production* (Hypogonadism) – (i) Hypergonadotrophic – Klinefelter's syndrome, castration, orchitis. (ii) Hypogonadotrophic – Isolated or part of panhypopituitarism.
   c. *Androgen insensitivity* (Testicular feminization).
   d. *Refeeding gynecomastia* – due to resumption of gonadotrophin production.
   e. *Miscellaneous* – Leprosy, paraplegia, generalised skin disease, ulcerative colitis, congestive heart failure, hypertrophic pulmonary osteoarthropathy, rheumatoid arthritis, Hodgkin's disease, myotonia dystrophica, leukaemia, chronic renal dialysis, familial.
3. **Pharmacological –**
   a. *Oestrogen therapy.*
   b. *Androgens.*
   c. *Digitalis, tetrahydrocannabinol, and griseofulvin* – bind to oestrogen receptors.
   d. *Anticancer drugs* – especially alkylating agents (testicular damage).
   e. *Anti-androgens* – including cyproterone acetate, spironolactone and cimetidine.
   f. *Other drugs* – Phenothiazines, reserpine, tricyclics, and methyldopa. (Mechanism unknown).

HICCOUGH

1. *Abdominal* – Transient following over-distension of stomach with food or drink or irritation of stomach, e.g. from alcohol. Peritonitis, diaphragmatic pleurisy, intestinal obstruction, after abdominal operations, subphrenic abscess, gastric dilatation, abdominal carcinoma, liver abscess, abdominal Hodgkin's disease, crisis (diaphragmatic) of tabes dorsalis.
2. *Thoracic* – Irritation of phrenic nerve, fibrous mediastinitis, cardiac enlargement, mediastinal tumours, adherent pericarditis, aortic aneurysm, oesophageal tumours.
3. *Cerebrovascular* – Tuberculous meningitis, encephalitis, brain tumour, hydrocephalus, multiple sclerosis, focal epilepsy, chorea, arteriosclerosis.
4. *Toxic* – Uraemia, diabetic ketoacidosis, severe systemic infections, anoxia, alcoholism, electrolyte imbalance.
5. *Functional* – e.g. following bouts of laughter or swallowing; or evidence of hysteria.
6. *Without demonstrable cause.*

Management –

1. *Removal or control of primary cause* – when possible.
2. *Physical or mechanical measures* – (a) Holding the breath. (b) Breathing in and out of a paper bag. (c) Compression of carotid sinus or eyeballs. (d) Stimulation of the pharynx to induce vomiting. (e) Drinking cold water, Valsalva manoeuvre, pull on the tongue. (f) Washing out the stomach if gastric dilatation.
3. *Drugs* – (a) Antispasmodics – (i) Octin – 10–15 drops of 10% solution in water or dragees, or subcutaneous or IM, may be repeated 3-hourly till satisfactory response. (ii) Atropine – 1/100 gr subcutaneously. (b) Chlorpromazine or promazine – 50 mg by mouth or IM. (c) Local anaesthetic orally – Xylocaine viscous one dessertspoon 1/2 hour after preliminary injection of atropine. (d) Baclofen 10 mg b.d. p.o. (e) Basal narcotic – Prolonged IV administration in resistant cases.
4. *Carbon dioxide* – Inhalation of 7% carbon dioxide in oxygen stimulates the respiratory centre.
5. *Phrenic nerve paralysis* – In rare cases, if hiccough tends to exhaust the patient, phrenic nerve block by paravertebral injection of 3–5 cervical roots, or nerve crush.

HOARSENESS OF VOICE

1. *Inflammation of larynx* – (a) Acute – Infection of larynx, acute epiglottitis, laryngotracheobronchitis, (b) Chronic – Nonspecific, polypoid laryngitis, vocal nodules.
2. *Chronic granulomas* – Tuberculosis, syphilis.
3. *Endocrine dysfunction* – Hypothyroidism.
4. *Mechanical interference with function* – Injury to larynx, tumours benign or malignant.

5. *Functional disorders* – Functional dysphonia.
6. *Laryngeal paralysis* – (a) *Central (intracranial) causes* – bulbar lesions, tumours or vascular lesions. (b) *Peripheral (in neck or thorax) causes* – stretching, compression or interruption of the recurrent nerve, usually the left, e.g. aneurysm of aorta, cardiac enlargement, achalasia, anthracosilicosis, bronchogenic carcinoma, carcinoma of oesophagus, thyroid or trachea. Trauma following thyroidectomy. Toxic neuritis – lead, arsenic, alcohol, measles, influenza, diphtheria.

HORNER'S SYNDROME

(According to site of lesion)

1. *Brainstem* – Tumour, vascular lesions.
2. *Spinal cord* – Syringomyelia, tumour.
3. *Spinal roots* (T_1, T_2) – Injury.
4. *Carotid artery* – Thrombosis.
5. *Sympathetic chain* – Apical lung carcinoma, glands.

HYPERPYREXIA

1. Malaria
2. Septicaemia
3. Lobar pneumonia
4. Pontine haemorrhage
5. Encephalitis
6. Heat stroke
7. Malignant hyperpyrexia
8. Dengue
9. Chikungunya fever

Hypersomnia (Attacks of drowsiness or sleep)

1. *Idiopathic narcolepsy*.
2. *Symptomatic narcolepsy* – Lesions in region of hypothalamus, e.g. increased intracranial pressure, encephalitis, brain injuries, multiple sclerosis.
3. *Hysteria.*
4. *Parasomnia* – in diabetic ketoacidosis, uraemia, portal systemic encephalopathy, or overdosage with sedative drugs.
5. *Klein-Levin syndrome* – Periodic attacks of hypersomnia with excessive hunger.
6. *Miscellaneous* – Hypopituitarism, hypothyroidism, severe anaemia, debilitating illness, anxiety neurosis.

HYPERTROPHIC OSTEOARTHROPATHY

1. *Pulmonary* – Ca bronchus, lymphoma, abscess, bronchiectasis, metastases.
2. *Pleural* – Fibroma, mesothelioma.
3. *Cyanotic congenital heart disease.*
4. *GI* – Ulcerative colitis. Crohn's disease, chronic dysentery, coeliac disease, lymphoma, Whipple's disease, biliary cirrhosis.
5. *Nasopharyngeal carcinoma.*

HYPERVENTILATION

1. *Anxiety or hysteria.*
2. *Pain.*
3. *Drugs* – Salicylates, analeptics, adrenaline.
4. *Increased metabolism* – Pyrexia, hyperthyroidism.
5. *Metabolic acidosis.*
6. *Anoxia*.
7. *Lung disease* – Atelectasis, pneumothorax, irritant gases.
8. *Hypotension.*

HYPOTENSION

1. *Symptomatic* – Addison's disease, Simmond's disease, shock, myocardial infarction, emphysema, pulmonary tuberculosis, etc.
2. *Constitutional permanent hypotension* – occurs in about 3% of healthy individuals; more common in females.
3. *Orthostatic hypotension* – Reduction of >20 mm Hg systolic BP and >10 mm Hg diastoloic BP on standing from lying within 3 minutes. Causes: Prolonged bed rest, prolonged use of hypotensives or major tranquilizers, β-blockers, vasodilators. Autonomic neuropathy, hyponatremia, Addison's disease, chronic kidney failure.

Management of postural hypotension –

1. Extra pillows under the head at night.
2. Extra sodium chloride in diet because salt causes retention of fluids in tissues which has a sort of binding effect on the capillaries.
3. Abdominal binder may help.
4. Drugs which raise blood pressure such as mephentermine sulphate 20–25 mg b.d. Amphetamine (5–10 mg.) may be useful.

IMPOTENCE

1. **Psychological** –
   a. *Developmental* – e.g. conflict in parent-child relationship.
   b. *Affective* – Depression, anxiety, guilt, inter-personal relationship.
   c. *Cognitional* – e.g. lack of knowledge about sex.

2. **Organic** –
   a. *Endocrine* – (i) Pituitary – Tumour, acromegaly. (ii) Thyroid – Hypothyroidism or thyrotoxicosis. (iii) Hypoparathyroidism. (iv) Diabetes mellitus. (v) Addison's disease. (vi) Testicular defects – Eunuchoidism, Klinefelter's syndrome, testicular feminization, interstitial cell tumour, ageing.
3. **Local conditions** – Priapism, Peyronie's disease, phimosis.
4. **Others** – (a) Extreme obesity. (b) Surgery, e.g. prostatectomy, bladder surgery. (c) Drug abuse and chronic alcoholism. (d) CNS disease –Parkinsonism, autonomic neuropathy, spinal cord injury. (e) Drugs – e.g. some antihypertensives, anticholinergics. (f) Hepatic or kidney failure. (g) Pelvic trauma.

INCREASED INTRACRANIAL PRESSURE

1. Mass lesion – Tumour, hematoma, abscess.
2. CSF accumulation – Hydrocephalus – Congenital, obstructive, following infection or haemorrhage.
3. Brain oedema –
   a. *Vasogenic* (vessel damage) – Tumour, abscess, contusion.
   b. *Cytotoxic* (Cell membrane pump failure) – Hypoxia, ischemia, toxins.
   c. *Hydrostatic* (High vascular transmural pressure) – e.g. post-brain decompression.
   d. *Hypo-osmotic* – Hyponatremia.
4. Brain swelling (Increased blood volume) –
   a. Arterial dilatation and hypertension.
   b. Venous congestion.
5. Benign intracranial hypertension.
6. Chronic meningitis or adhesive arachnoiditis and/ or aqueductal stenosis.
7. Thrombosis of cervical veins and dural sinus.
8. Addison's disease, hypoparathyroidism.
9. Excessive vitamin A and chloramphenicol therapy in children.
10. Withdrawal of corticosteroid therapy in children.

Intercostal Retraction or Suction

Bilateral:

1. Foreign body in larynx or trachea
2. Laryngeal diphtheria
3. Angioedema of glottis
4. COPD
5. Bronchiolitis
6. Bilateral diaphragmatic paralysis

Unilateral

1. Lung collapse from bronchial obstruction.
2. Unilateral lung fibrosis.

KAYSER-FLEISCHER RING

1. Wilson's disease.
2. Cryptogenic cirrhosis.
3. Chronic biliary cirrhosis
4. Prolonged cholestasis

KYPHOSCOLIOSIS

1. Congenital.
2. Idiopathic.
3. Rickets.
4. Rheumatoid arthritis.
5. Senile osteoporosis.
6. Neurological causes – Friedreich's ataxia, neurofibromatosis, syringomyelia, cerebral palsy, poliomyelitis.

LEG ULCERS

1. *Venous ulceration* – (a) Deep vein thrombosis. (b) Varicose veins. (c) 'Armchair legs' in elderly persons who sleep in a chair.
2. *Arterial insufficiency* – (a) Arteriosclerosis. (b) TAO.
3. *Neuropathy* – Diabetes mellitus, peripheral neuropathy.
4. *Vasculitis* – SLE, rheumatoid arthritis, PAN, Wegener's granulomatosis, erythema induratum, pyoderma gangrenosum.
5. *Systemic sclerosis.*
6. *Systemic hypertension* (Martorell's ulcer).
7. *Infection* – Leprosy, tuberculosis, tropical ulcer, postcellulitis, dermal leishmaniasis, syphilis, atypical mycobacterial infection.
8. *Blood disorders* – Sickle cell anemia, polycythemia vera, spherocytosis, DIC.
9. *Plasma protein disorders* – Cryoglobulinemia.
10. *Malignancy* – Basal cell carcinoma, squamous cell carcinoma (Marjolin's ulcer), reticulosis, malignant melanoma, dysproteinemia.
11. *Chilblains.*
12. *Trauma.*
13. *Frost bite*

Livedo Reticularis

A mottled net-like pattern of dilated blood vessels.

1. Idiopathic: Benign, complicated

2. Congenital: Cutis marmorata, telangiestatica marmorata
3. Secondary
   Vascular disease: Arteriosclerosis
   Vascular calcification
   Arteritis: PN, lupus erythematosus, RA, dermatomyositis, allergic granulomatosis
   Vascular occlusion: Emboli, thrombocythemia, intra-arterial injections.
4. Miscellaneous
   Paralysis
   Cardiac failure
   Tuberculosis
   Pancreatitis
   Syphilis
   Lymphomas
   Mycosis fungoides
   Amantadine therapy

Liver tenderness

1. Acute viral hepatitis
2. Liver abscess: amoebic, pyogenic
3. Congestive heart failure
4. Carcinoma liver
5. Drug-induced hepatitis
6. Infected hydatid cyst of liver
7. Budd-Chiari syndrome

Loin Pain

Renal:

1. Calculus, sloughed papilla.
2. Pyelonephritis, perinephric abscess.
3. Acute glomerulonephritis (esp. proliferative).
4. Vesicoureteric reflux.
5. Hemorrhage into cyst, infected cyst.
6. Segmental infarction (sickle cell disease, embolism).

Extra-renal:

1. Acute cholecystitis.
2. Acute pancreatitis.
3. Leaking duodenal ulcer (Rt. side).
4. High appendicitis.
5. Splenic rupture.
6. Acute porphyria.
7. Ectopic gestation.
8. Ileo-caecal carcinoma.

Loss of Memory

1. Transient – following concussion.
2. Epilepsy (intermittent forgetfulness).
3. Intracranial tumour esp. of frontal lobe, corpus callosum or temporal lobe.
4. Multiple sclerosis.
5. General paralysis and meningo-vascular syphilis.
6. Vitamin B_{12} deficiency.
7. Vitamin B_1 deficiency with or without Wernicke's encephalopathy, Korsakoff's psychosis.
8. Pellagra
9. Hypothyroidism
10. Huntington's chorea
11. Anticonvulsant and sedative drugs
12. Electroconvulsive therapy
13. Alcoholism
14. Senile cerebral atrophy
15. Hysterical or psychopathic
16. Rare diseases – Cerebral lipoidoses, gargoylism, Jakob-Creutzfeldt disease.

Lump in Left Iliac Fossa

1. Diverticular abscess
2. Ca colon
3. Crohn's disease
4. Pelvic (or transplanted) kidney
5. Lymphadenopathy (Iliac)
6. Faecal masses

Lump in Right Iliac Fossa

1. Appendicular abscess
2. Ileocaecal tuberculosis
3. Carcinoma of caecum
4. Amoeboma
5. Crohn's disease
6. Ectopic right kidney
7. Actinomycosis
8. Intussusception
9. Carcinoid syndrome
10. Lymphoma
11. Tubal pregnancy, ovarian tumour
12. Schistosomiasis

Macroglossia

1. Cretin
2. Acromegaly
3. Myxoedema
4. Down's syndrome
5. Haemangioma of tongue
6. Lymphangioma of tongue
7. Amyloidosis
8. Mucopolysaccharidosis
9. Glycogen storage disease

Mask-like Facies

1. Parkinsonism
2. Scleroderma
3. Hypothyroidism
4. Depression
5. Dementia
6. Myasthenia gravis
7. Facial myopathies
8. Bilateral UMN facial palsy

Melena (Tarry Stools)

1. *Swallowed blood.*
2. *Oesophageal and gastric causes* – (a) Ruptured oesophageal varices – cirrhosis of liver, portal hypertension. (b) Haemorrhagic gastritis. (c) Gastric ulcer or duodenal ulcer, or hiatus hernia.
3. *Intestinal causes* –
   i. Primary
      a. Carcinoma of intestinal tract.
      b. Typhoid fever.
      c. Crohn's disease.
      d. Amoebic dysentery.
      e. Ulcerative colitis.
      f. Colonic and sigmoid polyposis.
      g. Peptic ulcer in Meckle's diverticulum.
      h. Mesenteric infarction.
      i. Ankylostomiasis.
   ii. Secondary to systemic disease –
      a. Purpura and other haemorrhagic disorders.
      b. Polyarteritis nodosa.

Moon Face

1. Acute nephritis and nephrosis
2. Cushing's syndrome
3. Corticosteroid therapy
4. Superior mediastinal syndrome
5. Angioedema
6. Cri-du-chat syndrome
7. Congenital pulmonary stenosis

Morning Stiffness

1. Rheumatoid arthritis
2. Ankylosing spondylitis
3. Osteoarthritis
4. Myxoedema

Myoglobinuria

1. *Metabolic defects*
   A. Genetic –
      a. Deficiencies of glycolytic enzymes: Phosphorylase, LDH, phosphofructokinase, etc.
      b. Carnitine palmitoyl transferase deficiency.
   B. Sporadic –
      a. Exercise in excess of training
         i. Military recruitment, marathon runners, cross-country skiers
         ii. Status epilepticus, prolonged myoclonus, prolonged dystonia
         iii. Agitated delirium
         iv. High voltage electric shock, lightening stroke, electroshock therapy
      b. Excessive body temperature
         Heatstroke, malignant hyperthermia, malignant neuroleptic syndrome, infections
      c. Ischemia
         Thrombosis and embolism of major arteries and veins, sickle cell trait
      d. Drugs and toxins
         Alcohol, clofibrate and other fibrates, other hypolipidaemic drugs, heroin, LSD, opiates and barbiturates, azathioprine, 5-azacytidine
2. *Muscle necrosis*
   a. Crush
   b. Coma
   c. Toxic
3. *Loss of muscle membrane integrity*
   a. Toxic
      - Sea snake, tiger snake (Phospholipases myotoxins)
      - Hornet venom
      - Staphylococcal toxic shock syndrome
      - Drugs–succinylcholine
   b. Salt and water imbalances
      - Hypokalaemia (drugs, aldosteronism, renal tubular acidosis)

- Hypernatremia
- Hypophosphatemia
- Hyperosmolar non-ketotic states
- Acidosis (diabetic, renal tubular)

4. *Infections*
   1. Viral – influenza, coxsackie, ECHO
   2. Bacterial – staphylococcal, typhoid, legionella, clostridia
   3. Primary myopathies – Dermatomyositis, polymyositis

Nasal Regurgitation of Fluid

1. Bulbar and pseudo-bulbar palsy.
2. Acute bulbar paralysis – Myasthenic crisis, poliomyelitis, diphtheria, rabies, encephalitis, polyneuritis, botulism.
3. Polymyositis and dermatomyositis.
4. Muscular dystrophy.
5. Myotonia dystrophica.
6. Paralysis of tenth nerve by inflammatory, neoplastic or vascular lesion (posterior inferior cerebellar artery thrombosis).

Neck Pain

1. Mechanical disorders
   Spasmodic torticollis
   Cervical spondylosis
2. Systemic causes
   Inflammatory: Ankylosing spondylitis, RA, polymyalgia rheumatica
   Malignancy: Myeloma, metastatic Ca
   Infection: Staphylococcal or other sepsis, TB
   Metabolic: Osteomalacia
3. Whiplash injury
4. Fibromyalgia

Neck rigidity

- Meningitis
- Tetanus
- SAH
- Meningomyelitis
- Parkinsonism
- Parkinsonism
- Meningoencephalitis
- Meningism
- Rabies
- Intracranial haemorrhage (rare)
- Post. fossa tumour

Nodules (Subcutaneous)

1. Rheumatic nodules
2. Rheumatoid nodules
3. Multiple neurofibromatosis
4. Fibroma
5. Gouty tophi
6. Lepromatous leprosy
7. Sarcoid
8. Erythema nodosum
9. Xanthomatous deposits
10. Cysticercosis
11. Calcinosis
12. Heberden's and Bouchard's nodes
13. Haygarth's nodes
14. Osler's nodes
15. Metastatic carcinoma
16. Myositis ossificans progressiva
17. Mycosis fungoides
18. Dermal leishmaniasis
19. Syphilis
20. Tuberculosis cutis
21. Skin cancer

Non-pitting Oedema

1. Myxoedema
2. Elephantiasis
3. Chronic venous oedema
4. Milroy's disease
5. Scleroderma (early stage)
6. Sclerederma

Oculogyric Crisis

Involuntary acute ocular deviation usually upwards.

1. Post-encephalitic.
2. Parkinsonism.
3. Petit mal epilepsy.
4. Drug-induced – Phenothiazines.
5. Neurosyphilis.
6. Following head injury.

Oedema

1. **Oedema of venous origin** – *Pitting oedema:* (a) Ingestion of excessive salt. (b) Steroids. (c) Premenstrual. (d) Cardiac oedema. (e) Renal oedema. (f) Portal obstruction. (g) Obstruction of inferior vena cava. (h) Anaemia and hypoproteinemia. (i) Beriberi. (j) Epidemic dropsy. (k) Pregnancy. (l) Miscellaneous – Old age, dermatomyositis, Raynaud's phenomenon, disseminated lupus.

If pitting remains for more than one minute (slow oedema), congestion is the most likely cause. If the pitting disappears in 40 seconds (fast oedema), the cause is hypoalbuminemia.

2. **Lymphoedema** – *Non-pitting oedema* – due to lymph stasis.
   a. Congenital – Milroy's disease (primary lymphoedema), oedema of congenital arteriovenous aneurysm, congenital neurofibromatosis.
   b. Parasitic – filarial.
   c. Allergic – angio-oedema.
   d. Chronic inflammatory – repeated attacks of erysipelas.
   e. Post-traumatic – following fracture or soft-tissue injury.
   f. Post-operative – e.g. excision of axillary or inguinal malignant lymph nodes.
   g. Post-thrombophlebitic.
   h. Neoplastic – blockage of lymphatics by malignant tissue, e.g. cancer of breast.
   i. Lymphoedema or erythrocyanosis frigida – in young women with stout build whose legs are abnormally fat.
   j. Idiopathic or spontaneous – more common in females, spontaneous puffiness in ankle or foot, unilateral in majority, gradually extending up the leg over months or years. Oedema pitting at first, later becomes non-pitting.

Oral Manifestations of Systemic Disease

Teeth – (1) *Retarded eruption* – Congenital hypopituitarism or hypothyroidism, Down's syndrome, cleidocranial dysostosis, or after radiotherapy. Local causes, e.g. overcrowded arch. (2) *Loosening or early loss* – Dental caries or inflammatory periodontal disease, Down's syndrome, diabetes mellitus, neutropenia. (3) *Missing teeth* – in ectodermal dysplasia. (4) *Malformed teeth* – Local infection, trauma, radiotherapy. "Screw driver" teeth in congenital syphilis. Peg-shaped teeth in ectodermal dysplasia. (5) *Discoloration* – Tetracycline given during pregnancy or lactation, or to child under 12. Fluoride may cause white specs within the teeth. (6) *Dentinogenesis imperfecta* – may occur in isolation or in osteogenesis imperfecta.

Periodontal (Gingival) – (1) *Bleeding* –Purpura, acute leukaemia. (2) *Redness* – in gingivitis in pregnancy, females taking oral contraceptives, herpetic stomatitis, atrophic lichen planus or mucous membrane pemphigoid. (3) *Swelling* – Drugs, e.g. phenytoin, systemic disease, pregnancy. (4) *Pigmentation* – (i) Congenital – Racial, naevi, Peutz-Jeghers syndrome. (ii) Acquired – (a) Drugs – Antimalarials, phenothiazines, ACTH. (b) Endocrine – Addison's disease, ACTH producing tumours, Albright's syndrome, Nelson's syndrome. (c) Dental amalgam. (d) Melanoma. (e) Ulcers – Neutropenia.

Oral mucosa – (1) *Blisters* – Pemphigus, pemphigoid. Labial blisters in herpetic infection. (2) *Oral purpura* – Trauma, bleeding diathesis, infectious mononucleosis, rubella, amyloidosis, scurvy. Blood-stained crusting in erythema multiforme. (3) *Telangiectasia* in hereditary haemorrhagic telangiectasia or systemic sclerosis. (4) *Localised red areas* – lupus erythematosus, lichen planus or erythroplasia. (5) *Ulcers* – Infections – Herpetic stomatitis, chickenpox, infectious mononucleosis, tuberculosis, trigeminal herpes zoster, herpangia, syphilis, hand, foot and mouth disease. (i) Blood dyscrasias – Anaemias, leucocyte defects. (ii) Malabsorption – e.g. coeliac disease, Crohn's disease. (iii) Mucocutaneous diseases – lichen planus, pemphigoid, pemphigus vulgaris, erythema multiforme, lupus erythematosus. (iv) Drugs – e.g. cytotoxic drugs. (6) *Angular stomatitis* – Deficiency of vitamin B complex, iron or folic acid; malabsorption. Denture-induced. (7) Lumps – Benign tumours, lymphomas (in region of fauces), myeloma, histiocytosis and metastatic deposits.

White Oral Lesions

- Idiopathic keratosis
- Carcinoma
- Physical or chemical
  - Friction
  - Burns
  - Tobacco
  - Snuff
  - Sanguinarine
- Infections
- Candidiasis
- Hairy leukoplakia
- Syphilitic keratosis
- Papillomas (some)
- Mucocutaneous disease
- Lichen planus
- Lupus erythematosus
- Inherited lesions (such as white sponge naevus)

Red Oral Lesions

Widespread redness	Localised red patches
• Candidiasis	Candidiasis
• Iron deficiency	Erythroplasia
• Avitaminosis B	Purpura
• Irradiation mucositis	Telangiectases
• Lichen planus	Angiomas
• Mucosal atrophy	Kaposi's sarcoma
• Polycythaemia	Burns
	Lichen planus
	Lupus erythematosus
	Avitaminosis

Salivary manifestations – (1) *Dry mouth* – Drugs (anticholinergic or sympathomimetic), severe dehydration, Sjogren's syndrome, irradiation of salivary glands. (2) *Drooling of saliva* – Pharyngeal obstruction, parkinsonism, facial palsy, mental deficiency.

Halitosis – Poor oral hygiene, oral infections, dry mouth, starvation, drugs, e.g. penicillamine, systemic disorders such as lung infection (bronchiectasis, lung abscess), hepatic or renal failure, diabetic ketoacidosis and GI disease.

Changes in oral sensation – (1) *Loss of taste* – Dry mouth, irradiation of head and neck, drugs such as penicillamine, neurosis, maxillofacial injuries, cerebral metastases. (2) *Pain* – Local causes such as infection or dental carries, trigeminal neuralgia, migraine or giant cell arteritis, referred as in angina, or atypical facial pain psychogenic in origin. (3) *Sensory disturbances* – (a) Lingular or inferior alveolar nerve damage from trauma or removal of wisdom tooth, or peripheral or central neuropathies. (b) Intracranial lesions such as tumours, multiple sclerosis, syringobulbia. (c) Paget's disease. (d) Benign trigeminal sensory neuropathy. (e) Drugs – Labetalol, acetazolamide. (f) Hyperventilation or hysteria. (g) Mandibular osteomyelitis, leukaemic deposits or metastases may cause lower labial anaesthesia.

Orthopnoea

1. Cardiac: LV failure, pericardial effusion
2. Respiratory: Bronchial asthma, COPD, bilateral diaphragmatic palsy
3. Intra-abdominal: Large ascites, massive tumour
4. Renal: Nephrosis, acute nephritis, uraemia

Pallor

1. *Anemia* of any aetiology
2. *Peripheral vasoconstriction* – Shock, exposure to cold, common faint (syncope), extreme fright
3. *Dermal* – Thick skin, myxoedema, oedema

Palmar Erythema

A. **Physiological** – Pregnancy.
B. **Pathological** –
   1. Liver disease – Viral hepatitis, cirrhosis
   2. Rheumatoid arthritis, SLE
   3. Polycythemia
   4. Beriberi
   5. Mitral regurgitation
   6. Diabetes mellitus
   7. Chronic leukaemia
   8. Thyrotoxicosis
   9. Skin diseases – Tinea, eczematoid dermatitis, psoriasis, pityriasis rubra pilaris.

Palpitation

1. *Cardiac disease* – Ectopic beats, paroxysmal tachycardia, atrial flutter or fibrillation, ventricular tachycardia, heart block, hypertension and aortic regurgitation, associated with transient postural hypotension.
2. *Non-cardiac disease* – Effort syndrome, flatulent indigestion especially gall-bladder dyspepsia, anaemia, pulmonary tuberculosis, thyrotoxicosis, embarrassment of heart due to local pressure, e.g. pleural effusion, pneumothorax, tympanitis, ascites or pregnancy. Hypertensive crisis of pheochromocytoma.
3. *Non-organic disease* – After violent exertion or emotional upset specially in sensitive individuals, convalescence from a debilitating disease, excessive smoking, tea, coffee, or alcohol; functional cardiac arrhythmias, anxiety neurosis.

Paralysis of One Arm

Acute –

1. Cerebrovascular lesion.
2. Encephalitis.
3. Multiple sclerosis.
4. Poliomyelitis.
5. Neuritis.
6. Hysterical paralysis.

Chronic –

1. Tumour in arm area of brain, e.g. meningioma.
2. Lesions of brachial plexus – neoplastic compression, trauma at birth, cervical rib or scalenus anticus syndrome.
3. Syringomyelia.
4. Muscular dystrophy, motor neuron disease, polyneuritis may be confined to one limb for a time.

Paralysis of One Leg

Acute –

1. Thrombosis of paracentral artery
2. Multiple sclerosis
3. Cauda equina lesion
4. Sacral plexus lesion
5. Hysterical

Chronic –

1. Localized lesion of brainstem, e.g. multiple sclerosis
2. Parasagittal meningioma
3. Compressive or infiltrative lesion in dorsal or lumbar region of spinal cord
4. Brown-Sequard syndrome
5. Parkinsonism
6. Femoral or sciatic nerve palsy

Parotid Enlargement

(chronic, bilateral, nontender)

- Sjogren's syndrome
- Sarcoidosis
- Diabetes mellitus
- Cirrhosis
- Alcoholism
- Amyloidosis
- Acromegaly
- Uraemia
- Drugs (iodide, propylthiouracil)
- HIV infection

Pes cavus

1. Idiopathic
2. Spinocerebellar atrophy, e.g. Friedreich's ataxia, peroneal muscular atrophy
3. Spina bifida
4. Myelodysplasia in lumbosacral region
5. Sacral dermoid cyst with affection of cauda
6. Cerebral palsy
7. Poliomyelitis
8. Syringomyelia

Pigmentation of the Skin

1. *Yellow pigmentation* – (a) Jaundice. (b) Carotenemia – (no pigmentation of sclera and mucous membrane) results from excessive ingestion of foods rich in carotene such as carrots, oranges, squash, etc., lowered body metabolism, e.g. myxoedema. Simmond's disease and diminution of androgenic hormonal activity, e.g. the male castrate. (c) Administration of mepacrine. (d) Exposure to yellow industrial chemicals. (e) Ingestion of picric acid or its absorption from ointments applied to open wounds. (f) Diffuse xanthomatosis produces yellowish-orange type of skin discolouration.
2. *Haemoglobin pigmentation* – (a) Cyanosis. (b) Polycythemia. (c) Carbon monoxide poisoning (carboxyhemoglobinuria). (d) Methemoglobinaemia and sulphemoglobinaemia.
3. *Melanin pigmentation* – (see hypermelanosis).

Polyneuritis Cranialis

1. *Acute polyneuritis* – Involvement of several cranial nerves in association with polyneuritis of the nerves of the limbs.
2. *Inflammatory lesions within the skull* – Tuberculous meningitis, chronic syphilitic meningitis, osteomyelitis of the bones at base of skull, otitis media.
3. *Compression* – of multiple Ns. by neoplastic infiltration of meninges.
4. *Painful ophthalmoplegia.*

Priapism

Persistent and abnormal penile erection unaccompanied by sexual desire.

1. *Haematological* – Sickle cell disease, thalassemia, leukaemia, thrombocytopenia.
2. *Neurological* – Cerebral vascular accident, spinal cord injury.
3. *Local causes* – Penile trauma, perineal infection, myelomatosis, amyloidosis.
4. *Drugs* – Chlorpromazine, thioridazine, hydralazine, prazosin, reserpine, diazepam, anticoagulants and corticosteroids.
5. Alcoholism.
6. Idiopathic.

Prolonged (hung-up) Ankle Jerks

1. Hypothyroidism
2. Obesity
3. Gross oedema
4. Drugs – β-blockers, reserpine, quinidine, bromides
5. Diabetes mellitus
6. Arteriosclerosis
7. Sarcoidosis
8. Neurosyphilis
9. Parkinson's disease
10. Hypokalaemia
11. Myasthenia gravis
12. Profound hypothermia
13. Postpartum
14. Anorexia nervosa

Protein-losing Enteropathy

1. *Mucosal* – Coeliac disease, sprue.
2. *Inflammatory* – Inflammatory bowel disease, radiotherapy.
3. *Neoplasm* – Ca stomach, colon. Villous adenoma.
4. *Venous obstruction* – Cirrhosis, constrictive pericarditis, IVC obstruction.
5. *Lymphatic obstruction* – Lymphangiectasia, lymphoma, retroperitoneal fibrosis.
6. *Chronic arterial obstruction.*
7. *Infiltrate* – Whipple's disease, eosinophilic enteritis.

Proximal Myopathy

1. Cushing's syndrome.
2. Polymyositis/dermatomyositis.
3. Thyrotoxicosis.
4. Diabetes mellitus.
5. Malignancy.
6. Osteomalacia.
7. Hereditary muscular dystrophy.

Ptosis

1. Congenital.
2. Oculomotor nerve paralysis.
3. Horner's syndrome. (Ptosis less marked than in III n. palsy).
4. Tabes dorsalis.
5. Myasthenia gravis.
6. Ocular myopathy.
7. Myotonia dystrophica
8. Snake bite (Elapidae)
9. Periodic paralysis.

Puffiness of Face

1. Nephritic syndrome
2. Nephrotic syndrome
3. Angio-oedema
4. Myxoedema
5. Congestive heart failure
6. Hypoalbuminemia
7. Cushing's syndrome
8. Superior vena caval syndrome
9. Corticosteroid therapy
10. Lepromatous leprosy
11. Retro-orbital inflammation
12. Allergic dermatitis

Purpura

Non-Palpable Purpura

Ecchymoses: Chronic renal disease, clotting abnormalities, corticosteroids, Cushing's syndrome, primary amyloidosis, senile, trauma, venous stasis.

Dysproteinemia: Cryoglobulinemia, hyperglobulinaemia, macroglobulinemia.

Platelet abnormalities: Thrombocytopenia, thrombasthenia.

Progressive pigmentary purpura: Schamberg's dermatosis, Majocchi's disease, Lowenthal's disease.

Scurvy

Severe physical exertion

Wiskott-Aldrich syndrome., histiocytosis X.

Palpable Purpura

Sparse acral, palpable purpuric lesions

Atheroembolism

RA and SLE

Septicaemia: Gonococcal, meningococcal, candidial, pseudomonal, mucormycosis, staphylococcal

Subacute infective endocarditis

Multiple palpable purpuric lesions

Consumption coagulopathy: Drugs, post-infection, septicaemia, tumour.

Leukocytoclastic vasculitis: Allergy, collagen vascular disease, dysproteinemia, drug-related, Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura, vasculitis, Rocky Mountain spotted fever.

Quadriplegia

1. Brainstem lesion
2. Craniovertebral anomaly
3. High cervical cord compression or trauma
4. G-B syndrome
5. Acute anterior poliomyelitis
6. Myopathy
7. Myasthenia gravis
8. Periodic paralysis

Raynaud's syndrome

1. *Raynaud's disease.*
2. *Collagen diseases* – Rheumatoid arthritis, Sjogren's syndrome, polyarteritis nodosa, dermatomyositis and polymyositis, systemic sclerosis.

3. *Occlusive arterial disease* – Arterial embolism, thromboangiitis obliterans, subclavian compression in costoclavicular syndrome.
4. *Blood diseases* – Polycythemia vera, paroxysmal cold haemoglobinuria, high titre of cold agglutinins in blood, cryoglobulinaemia in association with lymphoma or myeloma.
5. *Poisoning by ergot.*
6. *Syringomyelia.*
7. *Trauma* (occupational) – pneumatic drill operators, grinders, riveters.

Rectal Bleeding

1. Haemorrhoids.
2. Perianal lesions.
3. Dysentery.
4. Inflammatory bowel disease.
5. Colonic diverticular disease.
6. Colonic polyps or cancer.
7. GI bleeding from drugs.
8. Ischaemic colitis.
9. Pseudomembranous colitis (following antibiotic use).
10. 'Gay bowel' syndrome in male homosexuals.
11. Irradiation proctitis.
12. Others – Ulcer of rectum, angiodysplasia, Meckle's diverticulum.

Recurrent syncope

1. *Cardiac syncope*
   a. Arrhythmia: Sinus node disease, AV node disease, tachycardia (particularly VT)
   b. Mechanical causes of reduced cardiac output: Extensive myocardial ischemia, AS, HOCM, rarely PS and pulmonary hypertension.
   c. Reduced ventricular filling: Pulmonary embolism, cough syncope, atrial myxoma/ball valve thrombus.
2. *Inappropriate vasodilatation*
   a. Vasovagal syncope: Simple vasovagal faint, malignant vasovagal syncope.
   b. Carotid sinus hypersensitivity
   c. Drug-induced: Anti-anginal, antihypertensive, neuroleptic medications.
   d. Orthostatic hypotension: Diabetes, Parkinson's disease, elderly
   e. Micturition syncope.
3. *Neurogenic syncope*
   a. Cerebral arrhythmia: Generalized motor seizures, temporal lobe epilepsy (associated with bradycardia).
   b. Reduced cerebral blood flow: Vertebrobasilar ischemia (drop attacks), carotid ischemia (in presence of vertebral artery disease).
4. *Metabolic*
   a. Systemic hypoxia: Recurrent pulmonary emboli
   b. Hypoglycemia: Diabetic on insulin/oral hypoglycaemic drugs.

Red face (Flushed Face)

1. Vasomotor instability.
2. Carcinoid syndrome.
3. Alcohol intake (with oral antidiabetic drug).
4. Steroids.
5. Acne rosacea.
6. Postmenopausal.
7. Dermatitis – Perioral, atopic, seborrhoeic, contact.
8. Psoriasis.
9. Lupus erythematosus.
10. Dermatomyositis.
11. Erysipelas.
12. Portwine stain.
13. Light sensitivity.

Restless Legs Syndrome

1. Abnormal iron metabolism
2. Uraemia
3. Diabetes mellitus
4. Rheumatic disease
5. Venous insufficiency
6. Genetic predisposition

Scaly skin

1. Ichthyosis
2. Psoriasis
3. Kwashiorkor
4. Pityriasis
5. Seborrhoeic dermatitis
6. Ring worm
7. Eczema
8. Lichen planus
9. Exfoliative dermatitis

Sialosis

(Painless, diffuse, non-tender, enlargement of parotid glands).

1. Idiopathic.
2. Sarcoidosis.
3. Alcoholic cirrhosis.
4. Diabetes mellitus.
5. Acromegaly.
6. Hyperlipoproteinaemia.
7. Chronic pancreatitis.
8. Drugs, e.g. phenylbutazone.
9. Anorexia nervosa.
10. HIV infection

Spider Naevi

1. Cirrhosis of liver.
2. Virus hepatitis (transient).
3. Pregnancy.
4. Normal individuals especially children (occasionally).
5. Rheumatoid arthritis.

Splinter fingers

1. Occupation trauma
2. Infective endocarditis
3. Trichinosis
4. Rheumatic fever
5. Infectious mononucleosis
6. Cryoglobulinemia
7. Severe hypertension
8. Severe rheumatoid arthritis
9. Widespread malignancy
10. Leukaemia
11. Scurvy
12. Idiopathic

Sterile Pyuria

1. Renal tuberculosis.
2. Drugs – Analgesic nephropathy, diuretics, jectofer.
3. Renal calculus.
4. Urogenital infection inadequately treated with antibiotics.
5. Amoebic infection of urinary tract.
6. Nonspecific urethritis (NSU).

Stridor

Noisy breathing with harsh, crowing sound mainly during inspiration and resulting from partial obstruction or narrowing of larynx, trachea or bronchus.

1. *Supraglottic* – Acute epiglottitis, angioedema, retropharyngeal abscess, infectious mononucleosis.
2. *Subglottic* – Acute laryngotracheitis, croup.
3. *Miscellaneous* – Foreign body aspiration, diphtheria, vocal cord palsy, pressure over main bronchus (from paratracheal and subcarinal lymph nodes).

Swelling in One Groin

1. Femoral hernia
2. Ectopic testis
3. Femoral lymphadenopathy
4. Saphenous varix
5. Psoas abscess
6. Femoral aneurysm

Swollen Leg

Acutely swollen leg

1. Trauma
2. DVT
3. Allergy
4. Cellulitis
5. Snake or insect bite
6. Rheumatological disease

Chronically swollen leg

1. Venous causes: Postphlebitic limb, varicose veins, venous compression
2. Lymphoedema: Primary, secondary
3. Congenital AV malformation
4. Dependency: Paralysis, arthritis, ischaemic rest pain

Tachypnoea

1. Pyrexia
2. Restrictive lung disease
3. Cardiac failure
4. Hypoxia
5. Pleuritic chest pain
6. Lobar pneumonia
7. Elevated diaphragm
8. Shock
9. Acidosis
10. Nervousness or hysterical

Thickened nerves (Hypertrophic neuropathy)

1. ***Hereditary*** –
   a. Neurofibromatosis.
   b. Charcot-Marie-Tooth disease.
   c. Dejerine-Sottas disease.
   d. Refsum's syndrome.
   e. Amyloidosis (Predominantly neuropathic forms).
2. ***Acquired*** –
   a. Leprosy.
   b. Acromegaly.
   c. Diabetes mellitus.
   d. Sarcoidosis.
   e. Relapsing neuropathies of unknown aetiology.

Tinnitus

1. *Ear disease* – (a) External ear – excessive wax, aural polypi or foreign body. (b) Middle ear – acute or chronic otitis media, Eustachian block. (c) Internal ear – Meniere's disease, specific fevers, extension of suppuration to labyrinth from middle ear, fracture base of skull.
2. *Auditory nerve* – Auditory nerve neuronitis, drugs such as streptomycin, salicylates; pressure from tumours or by new bone formation as in osteitis deformans.
3. *Pons* – Vascular or neoplastic lesions of lateral aspect.
4. *Cerebrum* – Temporal lobe epilepsy.
5. *General diseases* – Anaemia, leukaemia, AR, uraemia, arteriosclerosis with hypertension. During attacks of neuralgia or migraine.

Vascular Gangrene

Peripheral, Symmetrical

1. Asplenia
2. Immunosuppression
3. Diabetes mellitus
4. Kidney failure
5. Cold injury to extremities
6. Myoglobulinemia
7. Vasopressor drugs
8. Cerebral malaria
9. Viral gastroenteritis

Vesicular skin rashes

1. Eczema, cheiropompholyx
2. Herpes simplex
3. Herpes zoster
4. Impetigo
5. Scabies
6. Chickenpox
7. Dermatitis herpetiformis
8. Miliaria crystallina and rubra
9. Tinea
10. Drug eruption
11. Insect bites

Visual Failure

Transient monocular visual loss

1. Migraine
2. Retinal artery emboli
3. Recurrent hyphema
4. Recurrent angle closure
5. Optic disc anomaly
6. Blood dyscrasia
7. Papilloedema
8. Retinal vein occlusion
9. Primary antiphospholipid antibody syndrome
10. Compressive optic nerve lesion
11. Other optic neuropathy
12. Uhthoff's phenomenon – Diminution of vision with rise of temperature, e.g. after hot bath or exercise in demyelinating diseases of optic nerves.

Progressive loss of vision

1. Cataract.
2. Glaucoma.
3. Myopia.
4. Diabetic retinopathy.
5. Retinal degeneration – (a) Macular degeneration. (b) Retinitis pigmentosa.
6. Optic atrophy.
7. Toxic amblyopia – Chloroquine, tobacco, methyl alcohol, ergot, lead, arsenic.
8. Uveitis.

Blindness of abrupt onset

1. Assumed blindness usually in one eye.
2. Ischemic optic neuropathy.
3. Retrobulbar neuritis.
4. Leber's optic atrophy.
5. Inflammatory lesions of orbit – Pyogenic infections of paranasal sinuses or acute granulomatous infection of orbit.
6. Intracranial space-occupying lesions.
7. Poisons – Methyl alcohol.
8. Eclampsia.
9. Acute glaucoma.
10. Vascular occlusion of central retinal artery.
11. Cranial arteritis.

Vomiting (and Nausea)

Mechanism – Act of emesis is under the control of vomiting centre situated in the lateral reticular formation in medulla, and chemoreceptor trigger zone in the floor of the fourth ventricle. The vomiting centre receives afferent stimuli from the chemoreceptor trigger zone which can be activated by a number of stimuli such as bacterial toxins,

metabolic disturbances (e.g. uraemia), drugs and radiation. The efferent pathways are the phrenic nerves to the diaphragm, spinal nerves to intercostal and abdominal muscles and visceral efferent fibres in the vagus nerve to larynx, pharynx, oesophagus and stomach.

1. **Reflex** –
   a. Abdominal –
      Gastric – (i) Diseases – Acute and chronic gastritis, ulcer or carcinoma, pyloric spasm or stenosis, venous congestion as in portal obstruction and cirrhosis of liver. (ii) Chemical agents and poisons – food poisoning, corrosives and irritants, emetics like hypertonic salt solution, copper sulphate.
      Extragastric – Appendicitis, intestinal obstruction, spasm as in lead poisoning, intestinal worms, biliary and renal colic, pancreatitis, and due to stimuli arising from disease of urinary bladder or uterus, migraine.
   b. Peripheral – Stimulation of pharynx and fauces, severe trauma to testicle, muscles or joints. Primary shock.
2. **Central** –
   a. Special senses – Offensive smells, tastes, repulsive sights.
   b. Brain – Concussion, cerebral tumours or abscess, meningitis, cerebral haemorrhage, middle-ear disease, Meniere's disease, migraine, epilepsy; sea, train, car or air-sickness, radiation sickness.
   c. Spinal cord – Gastric crisis of tabes.
3. **Toxic** – Hepatic disease, uraemia, acidosis, alkalosis, hypoglycemia, excessive dehydration, toxaemia of pregnancy, cyclic vomiting of childhood. Drugs such as digitalis, emetine.
4. **Functional** or hysterical vomiting.

Morning vomiting –

1. Pregnancy or trophoblastic tumour.
2. Alcoholic gastritis.
3. Migraine.
4. Intracranial space-occupying lesion.

Weight loss (in an adult)

I. **Exogenous causes** –
   1. *Inadequate intake* –
      i. Anorexia and starvation, dietary fads, perverted appetite, chronic alcoholism, drug therapy, antibiotics.
      ii. Inability to swallow due to lesions of – (a) Tongue – paralysis, tumour, inflammation. (b) Palate – paralysis, tumours, inflammation, perforation. (c) Pharynx – paralysis, tumours, inflammation. (d) Oesophagus – stenosis, tumours, achalasia, foreign body, etc.
   2. *Inadequate absorption or utilization* – Chronic diarrhoea, lack of enzymes or bile, lack of hydrochloric acid and pepsin, malabsorption syndrome, intestinal parasites.
   3. *Excessive elimination or abnormal loss* – Diarrhoea, vomiting, fistulae, burns.

II. **Endogenous factors** –
   1. Endocrine disorders – (a) Addison's disease. (b) Thyrotoxicosis. (c) Diabetes mellitus. (d) Simmond's disease.
   2. Hepatic disorders – Cirrhosis of liver, liver abscess.
   3. Respiratory diseases – Pulmonary tuberculosis, chronic lung abscess, bronchiectasis.
   4. Blood diseases – Leukaemia, Hodgkin's disease.
   5. Cardiovascular – Malignant hypertension, subacute infective endocarditis.
   6. Kidney diseases – Chronic nephritis, pyonephrosis.
   7. Neurological disorders – Progressive muscular atrophy.
   8. Malignancy – Cancer stomach, bronchogenic carcinoma, etc.
   9. Psychosis – Depression, schizophrenia, anorexia nervosa.
   10. Drug addiction.
   11. Collagen diseases.

Weight loss in spite of increased appetite

1. Diabetes mellitus
2. Hyperthyroidism
3. Chronic kala-azar
4. Malabsorption syndrome

Xanthomas

1. Disorders of lipid metabolism.
2. Normolipaemic conditions: Histiocytosis X, xanthoma disseminate, diffuse planar xanthomatosis, juvenile xanthogranuloma, histiocytosis.

Xerostomia

1. Drugs (e.g. anticholinergics, antidepressants)
2. Rheumatoid arthritis

3. Sjogren's syndrome
4. Radiation therapy

Yawning

1. *Physiological,* e.g. boredom.
2. *Pathological* –
   a. Encephalitis.
   b. Epilepsy.
   c. Tumour in posterior fossa.
   d. Following nalorphine injection for opium poisoning.

23. THE FUNDUS

Changes in retinal vessels and retina –

1. ***Hypertensive retinopathy*** –

AV ratio	*Haemorrhages* (Normal 3:4)	*Exudates*	*Papilloedema*	
Gr. I	1:2	Nil	Nil	Nil
Gr. II	1:3	Nil	Nil	Nil
Gr. III	1:4	+	+	Nil
Gr. IV	Fine, fibrous cords	+	+	+

Malignant hypertension (Retinopathy) –

   a. Diffuse and marked contraction of retinal arteries.
   b. Swelling of optic nerve resembling papilloedema.
   c. Numerous flame shaped superficial haemorrhages.
   d. "Cotton wool" exudates in retina. (e) Star shaped figure at the macula.

2. ***Retinitis*** – Exudates and haemorrhages in the retina; the exudate interrupts the vessels. Papilloedema is a late sign. *Causes* – Hypertension, nephritis, diabetes, leukaemia and severe anaemia. In albuminuric retinitis there are large, flame shaped haemorrhages and cotton wool exudates. In diabetic retinitis the haemorrhages and exudates are usually small and round and hard (well defined), a mild degree of papilloedema may be present.
3. ***Retinal arteries*** —
   a. *Retinal haemorrhages* – (i) *Of haematological origin* – Diabetes mellitus, severe anaemia, bleeding diathesis, leukaemia, hypertension, papilloedema, trauma and retinal detachment, arteritis; rarely in polycythemia vera, and subacute infective endocarditis. (ii) *From venous congestion* – Compression of chest and head especially in newborn infants. (iii) *Subhyaloid (preretinal)* – Fluid level visible between retina and vitreous. Commonly found in subarachnoid haemorrhage; may be due to trauma to eye, malignant endocarditis, pyemia and septicaemia.
   b. *Embolism of central retinal artery* – Retina in the surrounding area becomes white, and because the choroid shows through the thinnest part of the retina, the macular region remains coloured yellow, orange or red – "cherry red spot".
   c. *Pulsation of retinal vessels* – In AR and in glaucoma, the arteries are seen to fill with each systole and collapse with diastole.
   d. *Arteriolar constriction* – Malignant hypertension, central retinal artery occlusion, retinitis pigmentosa, cinchonism.
4. ***Retinal veins*** –
   a. *Thrombosis of central retinal vein* – Outline of disc lost and large veins seen intermittently in the oedematous and haemorrhagic retina, as if a quantity of red paint had been splashed all over the retina.
   b. Dilated retinal veins – (i) Polycythemia, hyperviscosity. (ii) CRV thrombosis. (iii) Increased intracranial pressure. (iv) CO_2 retention. (v) Caroticocavernous fistula.
5. Takayasu's disease – Fragmentation of blood stream in the retinal vessels may be visible particularly when the patient is standing. Later ocular manifestations are atrophy of the retina and iris with neovascularization, the formation of retinal and microaneurysms and peri-capillary arteriovenous anastomoses and the rapid development of cataract.
6. Degenerations – (a) Retinitis pigmentosa – Laurence-Moon-Biedl syndrome, Refsum's disease. (b) Amaurotic family idiocy – Pale fundus with cherry red spot in macula; nerve head pale and atrophied. Similar picture may be seen in Niemann-Pick disease.
7. Septic retinitis – Small, round, white patches (Roth spots) often associated with small haemorrhages near the disc in SIE.
8. Tuberous sclerosis – Pale white mass on or very close to the nerve head, appearing like a small bunch of grapes.
9. Tumours – Neuroblastoma or metastatic tumours. Angiomatosis of retina may be associated with angioma in cerebrum or cerebellum.

10. ***Detachment of retina*** – may occur in severe inflammatory, exudative or degenerative process affecting the eye, in intraocular tumour and following trauma.
11. ***Angioid streaks*** – (breaks in Bruch's membrane): Paget's disease, acromegaly, pseudoxanthoma elasticum, Ehlers, Danlos syndrome, hereditary hypophosphatasia, sickle-cell anemia.

Choroid –

1. *Choroiditis* – Irregular areas of white sclera with dark patches of pigment epithelium: (a) Tuberculous – Minute miliary tubercles seen as discrete, widely separated, greyish white masses, pathognomonic of tuberculous meningitis or miliary tuberculosis. (b) Syphilis – Gummatous or multiple greyish-yellow dust-like vitreous opacities. (c) Toxoplasmosis. (d) Sarcoidosis.
2. *Vascular lesions* – Endarteritis may occur in syphilis.
3. *Tumours* – Melanomas or metastatic tumours.

Optic disc –

1. ***Papilloedema*** (Choked disc) – is a swelling of the nerve head. Diagnostic criteria – (a) Loss of physiological cup. (b) Elevation of disc head. (c) Blurring of disc margins. (d) Distended non-pulsatile veins. (e) Subhyaloid haemorrhages at disc margins.

Causes –

a. *Increased intracranial pressure* – due to space occupying lesion, or due to circulating block – aqueductal stenosis, intraventricular tumours, or outflow block of 4th ventricle.
b. *Cerebral oedema* – After head injury or cerebral anoxia, benign intracranial hypertension, vitamin A intoxication, steroid withdrawal, lead poisoning.
c. *Malignant hypertension*.
d. *Raised CSF protein or altered blood products* – Subarachnoid haemorrhage, chronic meningitis, Guillain-Barre syndrome, spinal cord tumours.
e. *Metabolic disorders* – Hypercapnia, hypocalcemia particularly in childhood, malignant exophthalmos.
f. *Circulation disorders* – CRV thrombosis, lateral sinus thrombosis, SVC obstruction, polycythemia rubra vera, multiple myelomatosis, macroglobulinaemia, hyperlipidemia, diabetes mellitus, vasculitis including temporal arteritis.

2. ***Papillitis*** – (Retrobulbar neuritis) – Oedema of nerve head, retinal veins engorged and tortuous, and haemorrhages. Poor visual acuity. *Causes* – (a) Infections – (i) Local – retinitis, periostitis. (ii) General – Syphilis, toxoplasmosis, typhoid, mumps, measles. (b) Toxins (toxic amblyopia) – tobacco, methyl alcohol, contraceptive pill, lead, carbon disulphide, thallium, quinine. (c) Demyelinating diseases – e.g. multiple sclerosis, Devic's disease. (d) Metabolic disorders – Diabetes, vitamin B_{12} deficiency. (e) Hereditary degenerative diseases – Friedreich's ataxia. (f) Giant cell arteritis.

The difference between papilloedema and papillitis:

- Examiner sees nothing (can't find the disc) but patient sees everything (normal vision) – Papilloedema
- Examiner sees nothing and patient sees nothing (severe visual loss) – Papillitis
- Examiner sees everything (normal looking disc) but patient sees nothing – Retrobulbar neuritis.

3. ***Optic atrophy*** –
   a. *Primary* (due to nerve damage) – Compression of optic nerve, post-neuritic, toxic, ischemic, infective (e.g. syphilis), hereditary (Leber's), traumatic.
   b. *Secondary* (following papilloedema) – Fuzzy appearance of nerve head. Disc appears like a tennis ball.
   c. *Consecutive* – to retinal disease, e.g. choroiditis, retinitis pigmentosa.
4. ***Tumours of optic nerve head*** – Neoplastic, inflammatory such as gumma or tubercle.
5. ***Congenital anomalies*** – Vascular, anomalies of pigmentation.

Retinopathy

Hypertensive	*Diabetic*
A V nipping	Microaneurysms
Flame haemorrhages	Dot and blot haemorrhages
Papilloedema	New vessel formation

24. SOME IMPORTANT LABORATORY VALUES

Haematology

(Also refer Chapter 5)

Reticulocytes – 25,000–75,000/c.mm. 25.75 × 10^9/1 (0.5-1.5% of erythrocytes).

Increased – (i) Response to Vitamin B_{12} therapy in primary macrocytic anaemia, (ii) congenital hemolytic jaundice, (iii) sickle cell anaemia, (iv) slight increase in leukaemia, myelophthisic anaemia, lead and mercury poisoning.

Decreased – Aplastic anaemia, myelodysplastic syndrome.

Mean corpuscular volume (MCV) 78–99 fl Red cell mass

- Males 31–35 mL/kg
- Females 20–30 mL/kg

Red cell half-life 25–33 days

MCV is most important of indices in presence of anemia. Low – Iron deficiency anaemia, thalassemia trait, anaemia of chronic disease. High – Vitamin B_{12} or folate deficiency, or one of the causes of macrocytosis, with normoblastic marrow. Normal MCV in anaemia – Acute blood loss, combined vitamin B_{12} and folate deficiency with iron deficiency or thalassemia trait, and in many primary haematological disorders such as hemolytic anaemia, myeloproliferative disorders and marrow infiltration.

Leucocytes

Leucocytosis (Neutrophilia) -

1. *Physiological* – (i) Newborn infant, (ii) following meals, (iii) strenuous exercise, (iv) convulsive seizures, (v) extreme heat or cold, (vi) pregnancy, (vii) emotional disorders, (viii) ultraviolet exposures, (ix) ether anaesthesia, (x) attack of paroxysmal tachycardia.
2. *Pathological* – (a) Infections – (i) Local –pneumonia, empyema, furunculosis, perinephric or appendicular abscess. (ii) General – septicaemia, infective endocarditis. (b) Toxic neutrophilia – (i) Endogenous intoxications – uraemia, eclampsia, gout, diabetic acidosis, burns. (ii) Drugs and poisons – Digitalis, mercury, lead, adrenaline, potassium chlorate, salicylates. (c) Post-haemorrhagic – especially haemorrhage into serous cavities – peritoneum, pleura, joints, subdural. (d) Associated with tissue destruction – myocardial infarction, postoperative, cancer of liver, gastrointestinal tract or bone marrow; burns, after haemolysis of red cells.

Lymphocytosis

1. *Infants and young children.*
2. *Infections* – (a) Viral: Infectious mononucleosis, infective hepatitis, acute infectious lymphocytosis, mumps, rubella, cytomegalovirus infection, varicella. (b) Bacterial: Tuberculosis, pertussis, brucellosis. (c) Protozoal: Toxoplasmosis.
3. *Lymphoproliferative disorders* – Chronic lymphocytic leukaemia, Waldenstrom's macroglobulinaemia.
4. *Miscellaneous* – Drug reactions, hyperthyroidism, myasthenia gravis, convalescence from any infection.
5. *Occasionally atrial myxoma.*
6. *Malaria.*
7. *Drugs* – Hydralazine, procainamide.

Eosinophilia –

Eosinophil counts up to 1.5 × 10^9/1

Common	Rare
Allergic rhinitis Hay fever	Inflammatory bowel disease
Extrinsic asthma	Some infectious diseases
Parasitic diseases	Neoplasms
Occupational lung disease	Skin diseases: Pemphigus, pemphigoid, dermatitis herpetiformis and psoriasis.

Eosinophil counts over 1.5 x 10^9/1

Common	Rare
Drug reactions	Vasculitis and granulomatous diseases
Intrinsic asthma	Neoplasms
Parasitic diseases	Hypereosinophilic syndromes
Pulmonary eosinophilia (including tropical eosinophilia)	

Monocytosis – (i) Certain bacterial infections – Tuberculosis, subacute bacterial endocarditis, brucellosis, typhus, and rarely typhoid. (ii) Protozoal infections – malaria, kala-azar, trypanosomiasis. (iii) Infectious mononucleosis. (iv) Hodgkin's disease. (v) Monocytic leukaemia. (vi) Tetrachlorethane poisoning.

Leukaemoid blood picture

A *leukaemoid reaction* is the occurrence in a patient suffering from a non-leukaemic disorder, of a peripheral blood picture resembling that of leukaemia, i.e. marked elevation of total white cell count or the presence of immature white cells, or both. Leukaemoid reactions may be either myeloid or lymphatic, or at times both (e.g. tuberculosis and carcinoma).

Neutrophilic leukaemoid reaction – (i) Hemolytic crisis in hemolytic anaemia. (ii) Haemorrhage. (iii) Hodgkin's disease. (iv) Infection – Tuberculosis (also lymphocytic), pneumo, meningo or staphylococcus infection, gas gangrene, diphtheria, leptospirosis, malaria, congenital syphilis (also lymphocytic). (v) Burns. (vi) Eclampsia. (vii) Mustard gas poisoning. (viii) Vascular thrombosis and infarction, e.g. mesenteric infarction. (ix) Marrow replacement by tumours including multiple myeloma, myeloid metaplasia.

Lymphocytic – Infectious lymphocytosis, infectious mononucleosis, pertussis, varicella.

Unfavourable signs in leucocytic picture -
(i) Extremely high total number of leucocytes with high percentage of neutrophils. (ii) Failure to develop leucocytosis. (iii) High proportion of immature cells, especially if they outnumber the mature forms. (iv) Absence of eosinophils. (v) Marked absolute reduction of lymphocytes. (vi) Presence of numerous toxic degenerative forms.

Leucopenia –

1. *Starvation or malnutrition.*
2. *Defective production* – (a) Hereditary – Infantile genetic agranulocytosis, familial benign chronic neutropenia, neutropenia with pancreatic dysfunction. (b) Acquired – (i) Ineffective myelopoiesis: Vitamin B_{12} or folate deficiency. (ii) Marrow infiltration: Leukaemia, myelofibrosis, carcinoma, myeloma, lymphoma. (iii) Drugs or irradiation.
3. *Excessive destruction* – (i) Isoantibody: Neonatal. Blood transfusion. (ii) Autoantibody: SLE, RA. (iii) Drug-dependent antibody: Amidopyrine.
4. *Other causes* – Hypersplenism, haemodialysis.

Immature forms – Myelocytes, myeloblasts or persistent large number of lymphocytes or immature forms indicates leukaemia.

Platelets –

Normal 15,000–350,000/c.mm. $150\text{-}350\times10^9$/l (Refer Ch. 4).

Positive LE cells in blood –

1. Systemic lupus erythematous (70-80%).
2. Rheumatoid arthritis (10%) and occasionally other collagen diseases.
3. Active chronic lupoid hepatitis (10%).
4. Atrial myxoma occasionally.

HLA antigens – Commonly associated disorders –

1. *Rheumatic diseases* – Ankylosing spondylitis and related disorders, rheumatoid arthritis.
2. *Neurologic diseases* – Multiple sclerosis, myasthenia gravis, olivopontocerebellar ataxia.
3. *Skin diseases* – Psoriasis, discoid lupus erythematosus, dermatitis herpetiformis, Behcet's disease.
4. *Endocrine diseases* – Insulin-dependent diabetes mellitus, Graves disease, subacute thyroiditis, Addison's disease, hypergonadotrophic hypogonadism, 21-hydroxylase deficiency.
5. *Gastrointestinal diseases* – Gluten-sensitive enteropathy, pernicious anaemia, chronic active hepatitis, hemochromatosis.
6. *Immunopathic diseases* – Atopy, complement deficiencies (C2, C4), SLE, Sjogren's disease.
7. *Malignant diseases* – Hodgkin's, acute lymphoblastic leukaemia, acute myelogenous leukaemia, nasopharyngeal carcinoma.
8. *Occupational disease* – Asbestosis.
9. *Drug reactions* – Hydralazine.

Erythrocyte sedimentation rate (ESR) –

	Adult males	*Adult females*
Wintergreen	3–5 mm. in 1 hour	4–7 mm. in 1 hour
Wintrobe	0–10 mm. in 1 hour	0–15 mm. in 1 hour

Normal values do not necessarily exclude disease.

Increased – (i) Physiological – pregnancy after the second month and menstruation. (ii) Infective disease – acute generalised and localised infections, chronic active infections like tuberculosis and rheumatic carditis. (iii) Ischemic disease – myocardial infarction. (iv) Metabolic – e.g. acute gout. (v) Traumatic – burns, fractures. (vi) Neoplastic – certain malignant tumours including Hodgkin's disease. (viii) Chikungunya fever.

Grossly abnormal ESR (>100 mm/h)

1. Multiple myeloma.
2. Carcinomatosis esp. active Hodgkin's.
3. Sepsis esp. florid TB.
4. Active vasculitis esp. giant-cell.
5. Severe anemia.
6. Uraemia.
7. Kala-azar.
8. SLE.

Low ESR (< 3 mm/h)

1. Polycythemia vera.
2. Sickle cell anemia.
3. Massive leucocytosis, e.g. CLL.
4. Hypofibrinogenaemia.
5. High-dose steroids or salicylates.
6. Congestive heart failure

No increase – Generalized blood infection without localisation, e.g. influenza, cystitis, sometimes infective process in CNS, fibrotic carcinoma or early sarcoma.

Value of ESR estimation –

a. *In diagnosis* (of little value) – (i) To distinguish functional from organic disease. (ii) Infective arthritis, acute gout and active rheumatoid arthritis cause an increase in the rate, but in osteoarthritis it is normal or only slightly increased. (iii) The rate is increased by pelvic inflammation but not with an unruptured ectopic gestation. (iv) The rate is always rapid in malignant pelvic tumours but not in simple pelvic tumours.

b *In prognosis and treatment* – (i) In fevers, a rising ESR suggests progress of the disease or onset of complications. (ii) In rheumatic fever, it is a specially sensitive index of persistent rheumatic infection (Cardiac failure gives falsely low and anaemia falsely high values). (iii) In acute nephritis, the rate remains high in patients passing into the chronic stage.

Ceruloplasmin and copper – Normal – Ceruloplasmin 27–37 mg/100 mL, Copper 70–140 mcg/100 mL (11–22 mol/L).

Elevated – Pregnancy, hyperthyroidism, aplastic anaemia, acute leukaemia, cirrhosis of liver.

Decreased – Wilson's disease.

Gammaglobulins (Immunoglobulins)

Immunoglobulin	Serum conc. mg/100 mL
IgG	800–1500
IgA	150–300
IgM	50–200
IgD	0–40
IgE	17–450 ng/mL

Hypergammaglobulinaemia –

a. *Diffuse 'broad band' type* – Chronic infection, cirrhosis of liver, collagen vascular disease, ulcerative colitis, Crohn's disease Hashimoto's thyroiditis.

b. *Narrow 'M band' type* – Multiple myeloma, Waldenstrom's macroglobulinaemia, 'benign' especially in old age. Leukaemia, Hodgkin's disease, carcinoma.

Hypogammaglobulinaemia –

a. *Primary* – Physiological in infancy, idiopathic, acquired, congenital sex-linked, alymphocytic, primary lymphopenic, associated with thymoma.

b. *Secondary* – (i) Protein deficiency – Malnutrition, malabsorption, nephrotic syndrome, protein-losing enteropathy, exfoliative dermatitis. (ii) Defective synthesis – Multiple myeloma, lymphoreticular disease, irradiation, cytotoxic drugs.

Fibrinogen – 0.2–0.4 g/100 mi (5.9-11.7 µmol/L).

Elevated – Glomerulonephritis, nephrosis (occasionally), and infectious disease.

Decreased – Accidents of pregnancy (placental ablation, amniotic fluid embolism, violent labour), acute and chronic hepatic insufficiency, congenital fibrinogenopenia, and occasionally with prostatic carcinoma.

C-reactive protein – (CRP) – Normal 0–20 g/mL It is an acute phase protein in acute rheumatic fever (unaffected by cardiac failure or anaemia) and most connective tissue diseases but in SLE there is a slight rise in CRP with disease activity. CRP levels rise normally with infection in SLE patients and this is useful in distinguishing disease activity from infection.

Plasma viscosity – Normal 1.50–1.72 centipoises.

Enzymes –

Alkaline phosphatase – Normal 5-13 KA or 2–5 Bodansky units per 100 mL

Increased – (i) Osteoblastic bone disease, e.g. osteitis fibrosa cystica, Paget's disease, osteogenesis imperfecta, severe osteomalacia, osteogenic sarcoma, metastatic carcinoma of bones. (ii) Hepatic duct or cholangiolar obstruction due to stone, stricture or neoplasm. Hepatic disease resulting from drugs such as chlorpromazine, methyltestosterone. (iii) Myeloid leukaemia. (iv) Hyperparathyroidism. (v) Hyperpituitarism. (vi) Physiological – pregnancy, alimentary hyperglycemia, ultra-violet light exposures, administration of irradiated ergosterol.

Decreased – Hypothyroidism, growth retardation in children.

Acid phosphatase – 0.5–2 units.

Increased – in carcinoma of prostate particularly with bone metastasis.

Amylase – 70–300 IU/L or 80–200 Somogyi units/100 mL

High level

Acute pancreatitis	Perforated peptic ulcer
Carcinoma pancreas	Ruptured ectopic
Mumps	Dissecting aortic
Salpingitis	aneurysm
Hepatic disease	Acute renal failure

Low level

Hepatitis	Pancreatic insufficiency
(Necrotizing)	Severe burns with liver
Toxaemia of	damage
pregnancy	

Lipase – 0–1.5 units.

Increased – Acute pancreatitis, carcinoma of pancreas, cholelithiasis with jaundice, cirrhosis or carcinoma of liver, intestinal obstruction, duodenal ulcer.

Transaminase enzymes — Glutamic oxalacetic transaminase (SGOT) 5–40 units. Glutamic pyruvic transaminase (SGPT) 5–35 units.

Elevated –(i) Hepatic disease – Hepatitis, cirrhosis of liver, hepatic congestion, metastatic carcinoma. (ii) Cardiac disease – Myocardial infarction. (iii) Miscellaneous – Skeletal muscle disease, haemolysis, acute pancreatitis, renal or cerebral necrosis, shock, pulmonary infarction, dermatomyositis, progressive muscular dystrophy, delirium tremens.

Creatinine phosphokinase (CPK) – 0–12 Sigma units/mL.

Elevated – In presence of muscle damage, e.g. myocardial infarction, trauma to muscle, progressive muscular dystrophy, polymyositis, and severe muscular exertion, delirium tremens, Endocrine causes - hypothyroidism, diabetic nephrotic syndrome. Penicillamine, Dermatomyosis/polymyositis.

Lactic dehydrogenase (LDH) – Normal – 150–450 units/mL.

Elevated – All conditions accompanied by tissue necrosis, particularly those involving acute injury of the heart, red cells, kidney, skeletal muscle, liver, lung and skin. Marked elevations accompany hemolytic anaemias, and the anaemias of vitamin B_{12} and folate deficiency, and polycythemia rubra vera. Although elevated in acute phase of infectious hepatitis, enzyme activity is seldom increased in chronic liver disease.

Serum aldolase – Normal 0–11 milliunits/ml (I.U.).

Elevated – Skeletal muscle disease, carcinomatosis, myeloid leukaemia, megaloblastic anaemia, hepatitis.

Serum myoglobin – Normal 6–85 pg/mL

Elevated – early in acute myocardial infarction.

Calcitonin – Normal less than 5 ng/mL

Elevated – Medullary carcinoma of thyroid, some patients with hyperparathyroidism.

Brain natriuretic peptide – normal up to 80 pg/mL Decreased in myocardial depression.

Arterial blood analysis

Analysis	Range
Bicarbonate	21–27.5 nmol/1
Hydrogen ion	36–44 nmol/1
PaO_2	12–15 kPa
$PaCO_2$	4.4–6.1 kPa
O_2 saturation	97% normally

25. RADIOLOGY

Chest Radiographs

Cardiovascular

Enlarged cardiac silhouette on chest radiograph

1. Chamber enlargement including:
   - Bradycardia
   - Athletes
2. Pericardial effusion
3. Spurious
   - Technical (rotated chest radiographs)
   - High diaphragm
   - Cardiac fat pads
   - Skeletal deformity (depressed sternum, scoliosis)
   - Racial (Afro-Carribeans)

Enlarged left atrium (Double right heart borders)

1. Mitral stenosis.
2. Mitral regurgitation
3. Congestive cardiomyopathy.
4. Ischemic heart disease.
5. Shunts (excluding ASD).
6. Left atrial myxoma.

Enlarged right atrium

1. *Volume overload* – ASD, TR, AV canal, APVD
2. *Pressure overload* – TS, RA myxoma
3. *Secondary to RV failure*

Enlarged left ventricle

1. *Volume overload* – MR, VSD, PDA, ASD with shunt reversal.
2. *Pressure overload* – MS, LA myxoma.
3. *Secondary to LV failure.*

Enlarged right ventricle

1. *Pulmonary hypertension.*
2. *Pressure overload* – PS.
3. *Volume overload* – ASD, VSD.
4. *Secondary to LV failure or mitral valve disease.*

Prominent main pulmonary artery

1. *Increased pressure*: Pulmonary arterial hypertension.
2. *Increased flow:* Shunts.
3. *Turbulence:* Pulmonary valve stenosis.
4. *Increased compliance*: Mycotic aneurysm (rare)
5. *Spurious*: Displaced by large aortic root, mediastinal mass, corrected transposition, projectional (lordotic/rotated).

Enlarged pulmonary arteries

Both central and peripheral vessels –

1. Left-to-right shunt (> 3:1).
2. Hyperdynamic circulation.

Only central vessels –

1. Vasoconstriction of peripheral vessels –
   a. COPD.

b. Secondary to venous hypertension, e.g. MS.
c. Secondary to left-to-right shunts.

2. Obliteration of peripheral arteries –
   a. Pulmonary embolism.
   b. Secondary to left-to-right shunts.
   c. Tumour emboli.
   d. Schistosomiasis.
   e. Primary pulmonary hypertension.
   f. Vasculitides, e.g. polyarteritis nodosa.

Pulmonary plethora

(Generalized increase in pulmonary vessel size – both arteries and veins)

1. Left to right shunts.
2. Veno-arterial mixing lesions: TAPVD, truncus arteriosus.
3. Cor pulmonale (mildly plethoric).

Globular (massive) cardiomegaly

1. Congestive heart failure.
2. Congestive cardiomyopathy.
3. Pericardial effusion.
4. Multiple valvular defects.
5. ASD with Eisenmenger's syndrome
6. Ebstein's anomaly

Cardiovascular calcification

Pericardium – Infective especially TB pericarditis.

Myocardium – Myocardial infarct, rheumatic heart disease (LA), mitral annular calcification.

Endocardium – Jet lesions.

Within chamber – Thrombus, myxoma.

Valve – Rheumatic heart disease, bicuspid-senile aortic valve, aortic homograft.

Coronary artery – Atheroma.

Pulmonary artery – Pulmonary arterial hypertension.

Aorta – Atheroma, aortitis.

Right sided aortic arch

1. Fallot's tetralogy.
2. Truncus arteriosus.
3. Pulmonary atresia with VSD.
4. Transposition of great vessels.
5. Tricuspid atresia – Rare.
6. Uncomplicated VSD – Rare.

Large aortic arch

1. Unfolding of aorta from atherosclerosis
2. AR: Prominent ascending aorta
3. Hypertension
4. AS: Post-stenotic dilatation
5. PDA

Pulmonary oedema with no increase in heart size –

1. Mitral stenosis.
2. Constrictive pericarditis.
3. Constrictive cardiomyopathy.
4. Blocked lung lymphatics, e.g. pneumoconiosis, silicosis.
5. Viral pneumonias.
6. Inhalation of toxic fumes.
7. Head injury or cerebrovascular accident.
8. Drowning.

Respiratory tract

Air bronchogram – When the normally aerated pulmonary parenchyma is replaced by non-aerated tissue, the bronchi and bronchioles become visible as branching, linear lucencies – the air bronchogram.

Causes of an air bronchogram

1. Pneumonia – infective, eosinophilic
2. Pulmonary oedema
3. Hemorrhage – traumatic/contusion, infarction, diffuse pulmonary hemorrhage
4. Radiation pneumonitis
5. Non-obstructive pulmonary collapse – Compressive atelectasis (e.g. pleural effusion), bronchiectatic collapse
6. Bronchoalveolar cell carcinoma
7. Lymphoma
8. Sarcoidosis
9. Cryptogenic organizing pneumonia
10. Alveolar proteinosis

Infiltrates

Upper zone infiltrates

1. TB, aspergillosis, Klebsiella pneumonia
2. Silicosis
3. Ankylosing spondylitis
4. Histiocytosis X
5. Radiation fibrosis
6. Hypersensitive pneumonitis (long-standing)

Lower zone infiltrates

1. Idiopathic pulmonary fibrosis.
2. Pulmonary fibrosis due to connective tissue disease.
3. Bronchiectasis.
4. Asbestosis.
5. Aspiration.
6. Cytotoxic-induced lung disease.
7. Pulmonary haemosiderosis.
8. Hypersensitivity pneumonitis.

Lung Consolidation

1. *Transudate (oedema)*
   - Cardiogenic, nephrogenic, neurogenic fat embolus
   - Inhalation of toxic or irritant gases, ARDS
   - Drug-induced
2. *Exudate*
   - Infective pneumonia
   - Eosinophilic lung disease (allergic aspergillosis, cryptogenic eosinophilic pneumonia)
   - Radiation damage
   - Connective tissue disorder
3. *Blood*
   - Contusion
   - Infarction
   - Diffuse pulmonary hemorrhage
4. *Alveolar cell carcinoma*
   - Neoplasm
   - Lymphoma
5. *Miscellaneous*
   - Alveolar proteinosis
   - Sarcoidosis
   - Fibrosing alveolitis

Honeycomb lung (Air-containing cysts)

1. Extrinsic allergic alveolitis.
2. Cystic bronchiectasis.
3. Collagen disorders – RA, scleroderma.
4. Pneumoconiosis (esp. asbestosis).
5. Cystic fibrosis.
6. Sarcoidosis.
7. Drugs – Busulphan, cyclophosphamide, bleomycin, melphalan, nitrofurantoin.
8. Histiocytosis X.
9. Tuberous sclerosis.
10. Neurofibromatosis.
11. Cryptogenic fibrosing alveolitis.
12. Lymphangitic carcinomatosis.

Lung Cavities

1. *Infection* – Tuberculosis. *Staph. aureus, Klebsiella pneumonia.* Aspiration. Actinomycosis. Histoplasmosis. Aspergillosis. Hydatid. Amoebiasis.
2. *Neoplastic* – Ca bronchus, metastases, Hodgkin's disease.
3. *Infarction* – more common in lower lobes.
4. *Lung abnormality* – Cystic bronchiectasis, infection of emphysematous bulla, bronchogenic cyst, sequestrated lung.
5. *Granulomas* – Rheumatoid nodules, Wegener's progressive massive fibrosis.
6. *Traumatic* – Hematoma, traumatic lung cyst.

Intracavitary Bodies

1. Mycetoma.
2. Hydatid (complicated).
3. Blood (laceration, tuberculosis, infarct).
4. Infection (abscess, necrotizing pneumonia).
5. Necrotic neoplasm (especially squamous).

Non-caseating Granulomas in Lung

1. Sarcoidosis
2. Brucellosis
3. Extrinsic allergic alveolitis
4. Chronic beryllium disease
5. Reaction to foreign body, e.g. IV drug abuse
6. Wegener's granulomatosis
7. Churg-Strauss syndrome
8. Lymphoid granulomatosis
9. Langerhans cell histiocytosis

Multiple Pulmonary Calcification

1. Infections – TB, chickenpox, pneumonia in childhood, histoplasmosis, coccidioidomycosis.
2. Mitral stenosis.
3. Silicosis, Caplan's syndrome.
4. Occupational lung disease.
5. Metastases.
6. Alveolar microlithiasis.
7. Hyperparathyroidism.
8. Hypervitaminosis D.

Hilar Enlargement

Unilateral –

1. Lymph nodes – (a) Infections – Tuberculosis (primary), pertussis, mycoplasma, histoplasmosis, coccidioidomycosis. (b) Lymphoma. (c) Ca bronchus. (d) Sarcoidosis.
2. Pulmonary artery – Post-stenotic dilatation (on left side), aneurysm, pulmonary embolism.
3. Mediastinal mass at hilum.
4. Pneumonia (Perihilar).

Bilateral –

Infection	Tuberculosis
	Histoplasmosis
	Infective mononucleosis
	Toxoplasmosis
	Mycoplasma, viral including HIV
	Chlamydial
Neoplasms / Infiltration	Lymphoma
	Leukaemia
	Metastasis
	Amyloidosis
	Histiocytosis
	Lymphomatoid lung disease
Inhalation	Silicosis
	Chronic beryllium disease
	Extrinsic allergic alveolitis
Obscure	Sarcoidosis

Bilateral Hilar Lymphadenopathy and Diffuse Pulmonary Shadowing or Infiltrates

- Tuberculosis
- Sarcoidosis
- Lymphoma
- Carcinoma
- Berylliosis
- Histoplasmosis
- Coccidioidomycosis
- Extrinsic allergic alveolitis.
- Pulmonary eosinophilia
- Bacterial or viral infection
- Drug reactions
- Histiocytosis X
- Pneumoconiosis
- Pulmonary hemorrhage

Miliary Calcification

1. Tuberculosis
2. Chickenpox
3. Histoplasmosis

Hilar Calcification

1. Tuberculosis.
2. Silicosis.
3. Sarcoidosis ("egg-shell" appearance).
4. Lymph node irradiation.
5. Histoplasmosis
6. Coal miner's pneumoconiosis.

Consolidation with Bulging of Adjacent Fissures

1. Abscess
2. Klebsiella pneumonia
3. Bronchogenic carcinoma

Unilateral transradiancy of hemithorax

Chest wall

- Mastectomy
- Absence of pectoralis major
- Poliomyelitis
- Poland's syndrome

Pleura

- Pneumothorax

Lung

- Emphysema
- Bullae
- Macleod's syndrome
- Compensatory hyperinflation – Post-lobectomy, lobar collapse
- Post-obstructive – has a vasoconstrictive component
- Pulmonary embolus

Bilateral transradiancy of hemithorax

A. ***Overexpanded lungs*** –
   1. Chronic obstructive pulmonary disease.
   2. Acute bronchiolitis.
   3. Stenoses – Tracheal, laryngeal or bilateral bronchial.

B. ***Normal or small lungs*** –
   1. Congenital heart disease with oligemic lung fields including pulmonary artery stenosis.
   2. Multiple pulmonary embolism.
   3. Primary pulmonary hypertension.
   4. Metastatic trophoblastic tumour.

Increased Density of Hemithorax

A. ***No shift of mediastinum*** –
   1. Massive consolidation.

2. Pleural effusion (in supine position).
3. Mesothelioma.

B. ***Mediastinal shift away from side of lesion*** –
1. Massive pleural effusion.
2. Diaphragmatic hernia.

C. ***Mediastinal shift towards side of lesion*** –
1. Massive collapse.
2. Pneumonectomy.
3. Lymphangitic carcinomatosis.
4. Pulmonary agenesis and hypoplasia.

Alveolar Opacities (Widespread)

1. Pulmonary oedema.
2. Pneumonia – TB, histoplasmosis, chickenpox, influenza, other viral pneumonias, pneumocystis carinii.
3. Haemorrhage – Trauma, anticoagulants, haemophilia, leukaemia, DIC.
4. Fat emboli.
5. Alveolar cell carcinoma.
6. Metastases (haematogenous).
7. Lymphoma (usually with adenopathy).
8. Sarcoidosis.
9. Loeffler's (Reversed bat's wing).

Nodules

Large nodules (more than 3 cm) –

1. *Neoplasm* –
   - Bronchial carcinoma
   - Metastasis
   - Lymphoma
   - Benign neoplasm (hamartoma).
2. *Granuloma* –
   - Tuberculous, fungal
   - Rheumatoid disease
   - Wegener's granulomatosis.
3. *Abscess* –
   - Pyogenic.
   - Hydatid disease.
4. *Congenital* –
   - Sequestered segment.
   - Bronchogenic cyst.
   - A-V malformation.
5. *Others* –
   - Hematoma
   - Infarct
   - Progressive massive fibrosis
   - Amyloidosis.

Medium-sized nodules (5–10 mm) –

1. Metastases.
2. Sarcoidosis.
3. Tuberculosis (bronchogenic spread).
4. Fungal infections.
5. Chickenpox pneumonia.
6. Abscesses.
7. A-V malformations.
8. Histiocytosis X.
9. Long-standing mitral valve disease (calcific nodules).

Miliary nodules (1–2 mm) –

1. *Soft tissue density* –
   - Miliary tuberculosis.
   - Sarcoidosis.
   - Coal workers' pneumoconiosis.
   - Fungal infections.
   - Extrinsic allergic alveolitis.
   - Haemosiderosis.
   - Oedema.
   - Metastases (uncommon).
2. *Calcific metallic density* –
   - Alveolar microlithiasis.
   - Siderosis.
   - Stannosis.

Solitary pulmonary nodule (coin lesion)

Malignant tumors

- Bronchogenic carcinoma
- Carcinoid
- Pulmonary lymphoma
- Plasmocytoma
- Pulmonary sarcoma
- Solitary metastasis (colon, breast, kidney, head and neck, germ cell, sarcoma, thyroid)
- Melanoma

Benign tumors

- Hamartoma
- Adenoma
- Lipoma

Infectious granulomas

- Tuberculosis
- Histoplasmosis
- Coccidioidomycosis

- Mycetoma
- Ascaris
- Echinococcal cyst
- Dirofilariasis

Noninfectious granulomas
- Rheumatoid arthritis
- Wegener's granulomatosis
- Sarcoidosis
- Paraffiinomas

Miscellaneous
- Abscess
- Silicosis
- Fibrosis/scar
- Haematoma
- Pseudotumour
- Spherical pneumonia
- Pulmonary infarction
- A-V malformation
- Bronchogenic cyst
- Amyloidoma

Miliary Pattern

Opacities with soft tissue density
- Miliary tuberculosis
- Fungal infection: Histoplasmosis, blastomycosis, coccidioidomycosis, farmer's lung.
- Coal miner's pneumoconiosis
- Acute extrinsic allergic alveolitis
- Varicella pneumonia
- Hyaline membrane disease in infants

Opacities with greater than soft tissue density
- Pulmonary haemosiderosis (from MS)
- Silicosis
- Siderosis
- Berylliosis

Discrete opacities
- Miliary carcinomatosis (from thyroid, melanoma). Enlarged lymph nodes
- Lymphoma
- Sarcoidosis

Opacities tending to coalesce
- Multifocal pneumonia
- Pulmonary oedema
- Extrinsic allergic alveolitis
- Fat emboli

High density opacities
- Post-lymphography
- Baritosis
- Stannosis

Other opacities
- Bronchiolitis obliterans
- Alveolar microlithiasis
- Wegener's granulomatosis

Multiple rounded pulmonary nodules
1. Pulmonary abscesses
2. Hydatid disease
3. Metastases
4. Coccidioidomycosis
5. Histoplasmosis
6. A-V malformations
7. Progressive massive fibrosis
8. Rheumatoid nodules
9. Caplan's syndrome
10. Wegener's granulomatosis

Pulmonary Cysts

1. Bleb/bulla
2. Bronchogenic cyst*
3. Hydatid cyst
4. Bronchiectasis
5. Laceration
6. Pneumatocoele

*Only when complicated by airway communication.

Unilateral Pulmonary Oedema

A. ***On same side as abnormality*** –
   1. Prolonged lateral decubitus.
   2. Rapid aspiration of fluid or air.
   3. Lung contusion.
   4. Unilateral aspiration.
   5. Bronchial obstruction.
   6. Shunts (systemic to pulmonary artery).

B. ***On opposite side of abnormality*** –
   1. Congenital hypoplasia of pulmonary artery.
   2. Thromboembolism.
   3. Unilateral emphysema.
   4. Lobectomy.
   5. Macleod's syndrome.

Septal Lines

1. Increased pulmonary venous pressure (Kerley's lines).
2. Lymphangitis carcinomatosa.
3. Lymphatic obstruction (hilar/mediastinal).
4. Diffuse fibrosis (pneumoconiosis, sarcoidosis).
5. Pneumonia (e.g. mycoplasma).
6. Pulmonary haemosiderosis.

Kerley's (septal) lines are caused by oedema of interlobular septae.

Kerley's A lines are seen in the upper zone (**A**pex) and also mid zone. They lie away from the pleural surfaces and point to the hila.

Kerley's B lines are more common than Kerley's **A** lines and occur most commonly in the **B**ase region (costophrenic angle). They are straight, short, (1–2 cm) horizontal lines that touch the parietal pleura. Septal B lines can be distinguished from vessels because:

- They do not branch
- They touch the pleura
- They are dense for their width

Kerley's C lines are seen usually near the **C**entre (mid zone) as fine interlacing lines which produce a 'spider web' appearance.

Unilateral Elevation of Hemidiaphragm

A. ***Causes above the diaphragm*** –
   1. Scoliosis
   2. Thoracic: Painful pleuritis, atelectasis, pulmonary embolus, rib fracture.
   3. Diaphragmatic: Phrenic n palsy, eventration, hernia.
   4. Abdominal: Mass, subphrenic infection, surgery.
   5. False: Subpulmonic effusion, chest mass.

B. ***Diaphragmatic causes*** – Eventration, hernia.

C. ***Causes below the diaphragm*** –
   1. Amoebic hepatitis or abscess, subphrenic abscess, splenic abscess and pancreatitis.
   2. Distended stomach or splenic flexure (left side).

D. ***General causes*** – Scoliosis, supine film.

Bilateral Elevation of Diaphragm

A. ***Causes above the diaphragm*** –
   1. Bilateral basal lung collapse.
   2. Fibrosis of lung with reduction in lung size.

B. ***Causes below the diaphragm*** –
   1. Ascites.
   2. Pregnancy.
   3. Hepatosplenomegaly.
   4. Large abdominal mass.
   5. Pneumoperitoneum.
   6. Bilateral subphrenic abscesses.

Bronchial Wall Thickening

1. Recurrent asthma/bronchitis (particularly children).
2. Bronchiectasis.
3. Cystic fibrosis.
4. Allergic aspergillosis.
5. Lymphangitis carcinomatosa.

Bilateral Basal Interstitial Opacities

1. Cryptogenic fibrosing alveolitis.
2. Fibrosing alveolitis: Systemic sclerosis, rheumatoid disease.
3. Asbestosis.
4. Drug-induced alveolitis (including nitrofurantoin).

Predominantly Upper Zone Fibrosis

(Linear and/or interstitial opacity)

1. Tuberculosis
2. Extrinsic allergic alveolitis
3. Silicosis
4. Sarcoidosis
5. Histiocytosis X
6. Ankylosing spondylitis
7. Allergic bronchopulmonary aspergillosis
8. Cystic fibrosis
9. Radiation fibrosis
10. Histoplasmosis, coccidioidomycosis.

Mediastinal Masses

I. ***Anterior mediastinum*** –

Upper region –
- Retrosternal goitre.
- Thymic mass.
- Aneurysm of ascending aorta.
- Tortuous innominate artery.

Mid region –
- Teratodermoids.
- Thymic mass.
- Sternal tumours – Primary or metastatic.

Lower region –
- Pericardial cyst.

- Pericardial fat pad.
- Localized eventration of diaphragm.
- Morgagni hernia.

II. ***Middle mediastinum*** –
- Aortic aneurysm
- Hilar nodes.
- Bronchogenic cyst.
- Aneurysm of aorta.
- Ca bronchus.

III. ***Posterior mediastinum*** –

Paravertebral region
- Neurogenic tumors
- Anterior thoracic meningocoele
- Abscesses, metastases, extramedullary haemopoiesis

Superior region
- Aneurysm of descending thoracic aorta
- Dilated oesophagus
- Neurenteric cyst

Inferior region
- Diaphragmatic hernia
- Hiatus hernia

Calcification of Chest

1. *Trachea-bronchi* – Senile.
2. *Pulmonary* – (a) Congenital – (i) Dermoid. (ii) Hamartoma, A-V aneurysm. (iii) Microlithiasis alveolaris pulmonale (familial). (b) Infections – (i) Tuberculosis. (ii) Histoplasmosis. (iii) Parasitic: Guinea worm, cysticercus. (c) Inhalation: Silicosis, asbestosis. (d) Neoplastic – (i) Primary: Bronchial Ca arising near or in TB focus. (ii) Secondary: Osteogenic sarcoma. (e) Broncholiths.
3. *Pleural* – Plaques following empyema, T.B., haemothorax, asbestosis, hyperparathyroidism, metastatic calcification.
4. *Mediastinal* – (a) Lymph glands – TB, sarcoid, pneumoconiosis. (b) Tumours – Thyroid adenoma, aneurysm, teratodermoid cyst.
5. *Cardiac* – Aortic arch, pericardium, valves or valve rings, thrombi, left atrium in MS, coronary arteries, patent ductus.
6. *Chest wall* – (a) Costal cartilage. (b) Healing rib fractures. (c) Tuberculous glands. (d) Osteomas and chondromas. (e) Soft tissue calcification – (i) Parasitic: cysticercosis, guinea worm, armillifer armillatus. (ii) Myositis ossificans. (iii) Breast tumours. (f) Intercostal arterial calcification (in renal osteodystrophy).

Oesophagus, Stomach, Abdomen

Diffuse Oesophageal Spasm

1. Atypical achalasia.
2. Gastro-oesophageal reflux.
3. Intermediate motor disorders.
4. Symptomatic oesophageal peristalsis.
5. Obstruction at the cardia.
6. Neuromuscular disorders (e.g. diabetes, motor neuron disease).

Malignant Stricture of Oesophagus

1. Short segment stricture with mucosal destruction.
2. 'Shouldering', the hallmark of malignancy in a tubular structure.
3. 'Apple-core' appearance as a result of 1 and 2.
4. No proximal dilatation.
5. Tracheo-bronchial opacification common (due to tracheo-oesophageal fistula, or regurgitation of contrast medium).

Giant Gastric Rugae

1. Malignancy, e.g. lymphoma, leiomyoma.
2. Gastrinoma.
3. Menetrier's disease (hyperproteinaemic hypertrophic gastropathy).

Jejunal Ulcers

1. Ulcerative jejunitis (malignant histiocytosis).
2. Coeliac disease, Crohn's disease.
3. Gastrinoma.
4. Meckel's diverticulitis.
5. Mesenteric ischemia, polyarteritis.
6. Lymphoma.
7. Infection – Typhoid, bacillary dysentery, TB, fungal, actinomycosis, syphilis.
8. Iatrogenic – Digoxin, potassium tablets.

Calcification (Radio-opacities) on an Abdominal X-ray

1. Faecoliths.
2. Phleboliths.
3. Calcified lymph nodes.
4. Calculi – Renal, biliary, prostatic.
5. Liver – Calcified hydatid, tuberculous, amoebic abscess, gumma, histoplasmosis, haemangioma, hepatoma, brucellosis.

6. Renal (urogenital) – Radio-opaque stone, renal tubular acidosis, secondary to hypercalcaemia, cortical necrosis, sponge kidney, tuberculosis, calcification in hypernephroma and polycystic kidneys. Prostatic calculi. Calcification of bladder tumours. Bilharziasis.
7. Spleen – Splenic stones, calcified cyst of spleen.
8. Pancreas – Chronic pancreatitis.
9. Suprarenal – Addison's disease, neuroblastoma or carcinoma.
10. Calcified aorta.
11. Calcified tumour – Dermoid, fibroid.
12. Foetus.
13. Calcification in abdominal wall – e.g. cysticerci.
14. Calcified tablets.
15. Calcified fibroid

Dilated Bowels

Mechanical obstruction of small bowel

Obstruction of large bowel

- Paralytic ileus
- Local peritonitis
- Small bowel infarction
- Toxic dilatation of colon (e.g. Crohn's disease)
- Gastroenteritis

Gas Outside Bowel Lumen

Gas under diaphragm

- Perforation of hollow viscus
- Laparotomy
- Miscellaneous: Pneumothorax, pneumomediastinum

Free Gas in Peritoneum

Gas in peritoneal cavity

- Perforation of GI tract (e.g. perforation of peptic ulcer)
- Laparotomy
- Colonic perforation

Signs

- Double wall sign of Rigler
- Umbilical ligament sign (Inverted V sign)
- Falciform ligament sign
- Urachus sign
- Triangle sign (gas trapped between three loops of intestine)
- Morrison's pouch sign over right. kidney
- Scrotal air sign (in head low position)
- Football sign (air rising to the abdomen, best seen in children).

Gas in Wall of Bowel

- Pneumatosis coli (bubbles of gas)
- Infarction of bowel (linear streaks)
- Necrotizing enterocolitis

Hepatic Calcification

1. Amoebic abscess.
2. Tuberculosis.
3. Hepatoma.
4. Hydatid cysts.
5. Brucellosis.
6. Gumma.
7. Haemangioma.
8. Histoplasmosis.
9. Intrahepatic biliary calculi.

Pancreatic Calcification

1. Alcoholic pancreatitis.
2. Hyperparathyroidism.
3. Pancreatic pseudocyst.
4. Cystic fibrosis.
5. Kwashiorkor.
6. Hereditary pancreatitis.
7. Neoplasms – Cystadenoma and cystadenocarcinoma.
8. Chronic tropical calculous pancreatitis
9. Idiopathic.

Acute Pancreatitis

Plain abdominal radiograph

- Gasless abdomen: Very few gas shadows seen
- Localized ileus in region of maximum inflammation
- Colon cut-off sign: Abrupt cut-off of gas shadow of transverse colon near the flexure
- Left sided pleural effusion may occur
- Obliteration of pro-peritoneal fat line may be seen
- Pancreatic calcification in presence of above signs would suggest acute-on-chronic pancreatitis.

Urinary Tract

Small Kidneys

Unilateral:

1. *Scarred kidney* –
   - Chronic pyelonephritis/Reflux nephropathy.
   - Tuberculosis.
   - Infarction (Lobar).
   - Renal dysplasia.

2. *Smooth kidney* –
   - Post-obstructive atrophy.
   - Ischemia (Renal artery stenosis).
   - Following renal infarction.
   - Radiation nephritis.
   - Congenital hypoplasia.

Bilateral (Small smooth kidneys):

1. Chronic glomerulonephritis.
2. Chronic papillary necrosis.
3. Hypertension.
4. Obstructive uropathy.
5. Renal artery stenosis.
6. Arteriosclerosis.

Large Kidneys

Unilateral:

1. Compensatory hypertrophy.
2. Obstructed kidney.
3. Pyonephrosis.
4. Tumour.
5. Polycystic kidney.
6. Acute pyelonephritis.
7. Hematoma.
8. Renal vein thrombosis.
9. Acute infarction.
10. Duplex kidney.

Bilateral:

1. *Proliferative and necrotizing disorders* – Acute glomerulonephritis, PAN, Goodpasture's syndrome, Wegener's granulomatosis, SLE.
2. *Abnormal protein infiltration* – Amyloid, multiple myeloma.
3. *Fluid accumulation* – Acute tubular or cortical necrosis.
4. *Infiltration* – (a) Neoplastic – Lymphoma, leukaemia. (b) Inflammatory – Acute interstitial nephritis.
5. *Miscellaneous* – Renal vein thrombosis, polycystic kidneys, acute papillary necrosis, bilateral hydronephrosis, sickle cell anaemia, medullary sponge kidneys. Gigantism and acromegaly.
6. *Diabetes mellitus*

Solid Renal Masses

1. Renal cell carcinoma.
2. Metastatic deposits.
3. Transitional cell carcinoma.
4. Haematoma.
5. Unusual masses – Tuberculoma, lymphoma, focal xanthogranulomatous pyelonephritis, angio-myolipoma, juxtaglomerular tumour, sarcoma.

Renal Calcification

1. Renal stones.
2. Due to localized disease – (a) Infections – Tuberculosis, abscess, hydatid. (b) Carcinoma. (c) Renal artery aneurysm.
3. Nephrocalcinosis –
   a. *Medullary* – Hyperparathyroidism, renal tubular acidosis, medullary sponge kidney, renal papillary necrosis, hypercalcaemia or hypercalciuria, oxalosis.
   b. *Cortical* – Acute cortical necrosis, chronic transplant rejection, chronic glomerulonephritis (rare).

Skull and Bone Radiographs

Punched-out Translucencies in Skull

Physiological –

1. Arachnoid granulations (parasagittal)
2. Emissary parietal foramina
3. Parietal fenestrae
4. Increased convolutional markings.

Pathological –

1. Myelomatosis.
2. Hyperparathyroidism.
3. Metastatic deposits from thyroid, bronchus, breast or kidney.
4. Leukaemias.
5. Sickle-cell anaemia.
6. Cushing's syndrome
7. Histiocytosis.

Increased Density of Skull Vault

Localized

- Sclerotic metastases
- Paget's disease
- Osteoma
- Hyperostosis
- Fibrous dysplasia

Generalized

- Sclerotic metastases
- Paget's disease

- Acromegaly
- Osteopetrosis
- Myelosclerosis

'Hair-on-end' Skull Vault

1. *Hemolytic anaemias* –
   - Thalassemia
   - Sickle-cell anaemia
   - Spherocytosis
   - Elliptocytosis
2. *Neoplasms* – Haemangioma, meningioma, plasmocytoma, metastases of neuroblastoma, rarely osteosarcoma.
3. *Miscellaneous* – Cyanotic heart disease, severe iron deficiency anaemia in childhood. Hereditary spherocytosis, elliptocytosis, pyruvate kinase deficiency.

Enlarged Pituitary Fossa

1. Intrasellar or parasellar tumour –Pituitary adenoma, craniopharyngioma, prolactinoma, meningioma, aneurysm.
2. Raised intracranial pressure.
3. Empty sella syndrome – Defect or distortion of diaphragma sellae.
4. Nelson's syndrome:

Empty Sella Syndrome

A. *Primary*
   1. Congenital absence of diaphragmatic sella
   2. Herniation of subarachnoid space into sella
   3. Involution of pituitary (a) Physiological after pregnancy and after menopause. (b) Pathological in Sheehan's syndrome or infarction of pituitary in vasculitis, diabetes, head injury, meningitis.
   4. Rupture of suprasellar or parasellar cyst.

B. *Secondary*
   1. Pituitary surgery, ablation or radiation.
   2. Ischemia after childbirth.
   3. Head trauma.

Intracranial Calcification

Unifocal –

1. *Familial*
2. *Physiological* – Pineal, choroid plexus.
3. *Pathological* –
   a. Neoplasms – Glioma, meningioma, craniopharyngioma, chordoma, metastases, pinealoma, lipoma, teratoma, dermoid, etc.
   b. Vascular – Atheroma, aneurysm, A-V malformation, chronic subdural hematoma, healed infarct, Sturge- Weber syndrome.
   c. Infections – Tuberculoma, abscess.
   d. Extracerebral – Foreign body, calcified sebaceous cyst, osteoma of calvarium.

Multifocal –

1. *Infections* – Cysticercosis, toxoplasmosis, hydatid, cytomegalovirus rubella, tuberculoma, histoplasmosis, torulosis, etc.
2. *Metabolic* – Hypoparathyroidism, vitamin D intoxication, chronic renal failure, lead or carbon monoxide poisoning.
3. Tuberous sclerosis.

Calcification of basal ganglia

1. Secondary hypoparathyroidism, pseudo-hypoparathy roidism.
2. Perinatal asphyxia.
3. Cockayne's syndrome
4. Tubosclerosis
5. Familial idiopathic

Bones

Punched-out erosions in extremity bones

1. Gout
2. Rheumatoid arthritis
3. Psoriatic arthritis
4. Osteoarthritis
5. Sarcoid
6. Multiple myeloma
7. Hand-Schüuller-Christian disease
8. Hyperparathyroidism
9. Leprosy
10. Miscellaneous – Gaucher's, Albright's (polyostotic fibrous dysplasia), osteitis fibrosa cystica, aneurysmal bone cysts, non-ossifying fibroma.

Periosteal Calcification

1. Subperiosteal haemorrhage.
2. Following a fracture.
3. Bone infection – Tuberculous, pyogenic or syphilitic.
4. Pulmonary osteoarthropathy.
5. Bone neoplasms and secondary deposits.

Generalized Increase in Bone Density

1. Myelosclerosis.
2. Developmental osteopetrosis (Marble bone disease).
3. Renal osteodystrophy.

4. Fluorosis.
5. Secondary deposits.
6. Paget's disease (Commonly multifocal).

Sacroiliitis

1. Ankylosing spondylitis.
2. Other seronegative arthritides – psoriatic, Reiter's, juvenile chronic arthritis.
3. Inflammatory bowel disease.
4. Infection – septic arthritis, TB, brucellosis.
5. Recurrent polyserositis.
6. Ochronosis.

Expansible Bone Lesions

1. **Non-neoplastic** –
   (a) Hydatid. (b) Fibrous dysplasia. (c) Hyperparathyroidism (brown tumour). (d) Haemophilic pseudotumour.
2. **Benign neoplasms** –
   a. Giant cell tumour.
   b. Aneurysmal bone cyst.
   c. Endochondroma.
3. **Malignant neoplasms** –
   a. Metastases
   b. Plasmocytoma
   c. Chondrosarcoma
   d. Fibrosarcoma

Distal Phalangeal (tuft) Resorption

1. Neuropathic – Leprosy, syringomyelia, diabetes, myelomeningocoele
2. Scleroderma
3. Psoriatic arthropathy
4. Thermal injuries
5. Trauma
6. Hyperparathyroidism
7. Epidermolysis bullosa
8. Raynaud's disease

Rib Notching

A. **Superior surface** –
   1. *Connective tissue diseases* –
      - Rheumatoid arthritis
      - SLE
      - Scleroderma
      - Sjogren's syndrome
   2. *Metabolic* – Hyperparathyroidism
   3. *Miscellaneous* –
      - Neurofibromatosis (Ribbon ribs)
      - Marfan's syndrome
      - Restrictive lung disease
      - Poliomyelitis
      - Osteogenesis imperfecta
      - Progeria

B. **Inferior surface** –
   1. *Arterial* –
      - Coarctation of aorta (4th to 8th ribs)
      - Aortic thrombosis (bilateral notching of lower ribs)
      - Subclavian obstruction (first 4 ribs)
      - Pulmonary oligaemia
   2. *Venous* – Superior vena cava obstruction.
   3. *Arteriovenous* – Pulmonary or chest wall A-V malformation
   4. *Neurogenic* – Neurofibromatosis.

Focal Rib Lesion (Solitary or Multiple)

1. **Neoplastic** –
   - *Metastases* – (i) Adult male – bronchus, kidney or prostate. (ii) Adult female –breast. (iii) Child – Neuroblastoma.
   - *Primary malignant* – Multiple myeloma, plasmocytoma, chondrosarcoma, Ewing's tumour (child).
   - *Benign* – Osteochondroma, enchondroma, histiocytosis X.
2. **Non-neoplastic** –
   - Healed rib fracture
   - Fibrous dysplasia
   - Paget's disease
   - Brown tumour of hyperparathyroidism
   - Osteomyelitis (tuberculous, bacterial or fungal).

Spine
Tuberculous Spine

1. Decreased intervertebral disc space
2. Some degree of collapse of diseased vertebra with anterior wedging
3. Paravertebral soft shadow due to paravertebral abscess.

Radiological classification: Types –

- Marginal type – Paradiscal pattern of involvement. Reduction of disc space is early sign. Formation of

paravertebral abscesses seen as soft tissue shadows in relation to affected vertebra – either fusiform (bird's nest' abscess) or globular in case of tense abscess. Ultimately, destruction of the vertebra causes it to collapse resulting in anterior wedging of the vertebra. A gibbus occurs if more than one vertebra is affected.

- Central type: Normal intervertebral disc but presence of central abscess.
- Anterior type: An anterior located abscess is seen which tracks along the anterior longitudinal ligament. Erosions over anterior surface of the vertebral bodies, resembling erosions due to aortic aneurysms (aneurysmal sign). Ribs near the affected vertebrae show lytic lesions.

Erosion of vertebrae: Scalloping of vertebral bodies –

Anterior:

- Tuberculous spondylitis: Erosion of vertebral bodies, decreased intervertebral disc space, and paraspinal soft tissue shadows, which makes the spinal column appear widened.
- Lymphadenopathy: Well defined margins of erosions (except malignant infiltration of vertebrae).
- Aortic aneurysm: Well-defined margins of erosions. Calcification of the aneurysm may be visualized as an arcuate line. Normal disc spaces.

Posterior:

- Spinal tumors: Meningioma, lipoma, dermoids, ependymoma
- Neurofibromatosis: (a) Posterior scalloping due to mesodermal dysplasia and associated ductal ectasia. (b) Localized scalloping due to pressure of neurofibroma. (c) May be associated widening of adjacent intervertebral foramen and flattening of a pedicle
- Achondroplasis: Breaks in anterior aspect of vertebral bodies, and spinal stenosis
- Acromegaly: Associated osteoporosis, calcified discs, spur formation and increase in anteroposterior and transverse diameters of vertebral bodies
- Syringomyelia
- Hydrocephalus (communicating)
- Marfan's syndrome
- Ehlers-Danlos syndrome
- Hurler's syndrome
- Morquio's syndrome.

Neoplasm

Spinal cord and meninges:

1. Erosion of vertebral body or pedicles
2. Enlargement of intervertebral root of foramina
3. Vertebral: Metastases, haemangiomas, aneurysm, bone cysts, multiple myeloma.

Single Collapsed Vertebra

1. Trauma
2. Infection – Tuberculosis
3. Neoplasm – (a) Benign – Giant cell tumour, haemangioma, bone cyst. (b) Malignant – Metastasis, lymphoma, multiple myeloma
4. Osteoporosis
5. Histiocytosis

Multiple Collapsed Vertebrae

1. Osteoporosis.
2. Neoplasms – Metastases, myeloma.
3. Trauma.
4. Infection – Pyogenic or tuberculous.
5. Histiocytosis.
6. Sickle cell anaemia.
7. Scheuermann's disease.

Metabolic Bone Disease

1. Rugger-jersey spine
   Renal osteodystrophy
   Osteopetrosis.
2. 'Ivory vertebrae'
   Paget's disease
   Hodgkin's disease
3. 'Codfish' vertebrae
   Osteoporosis
   Osteomalacia
   Sickle-cell disease

Arthritis Mutilans

1. Rheumatoid arthritis
2. Juvenile chronic arthritis
3. Psoriatic arthropathy
4. Neuropathic arthropathy
5. Leprosy
6. Diabetes mellitus
7. Reiter's syndrome

Fluorosis

Milky white appearance of:

- Atlas and axis (lateral view)
- Pelvic bones, lumbar and sacral vertebra and femur
- Calcification of interosseous membrane and milky white appearance of bones of forearm.

Soft Tissue Calcification

Linear and curvilinear –

1. Nerve – Leprosy, neurofibromatosis.
2. Artery – Atherosclerosis, diabetes, hyperparathyroidism.
3. Ligament – Fluorosis, ankylosing spondylitis, tendinitis, alkaptonuria, diabetes.
4. Parasitic – Guinea worm, cysticerci, Loa loa, armillifer.

Conglomerate –

1. Collagen disorders – Scleroderma, dermatomyositis.
2. Metabolic – Hyperparathyroidism, gout (tophi).
3. Traumatic – Haematoma, myositis ossificans.
4. Tuberculous lymph node or abscess.
5. Neoplasm – (a) Benign – Periosteal lipoma, haemangioma. (b) Malignant – Periosteal osteosarcoma, liposarcoma.

Urinary Tract

Calcified Renal Shadows

1. Renal calculi
2. Tuberculous calcification
3. Renal abscesses
4. Hydatid cyst
5. Renal artery aneurysm
6. Nephrocalcinosis
7. Medullary sponge kidney ('bunch of grapes' appearance)
8. Renal tubular acidosis
9. Xanthogranulomatous pyelonephritis
10. Hyperparathyroidism (renal medullary)
11. Carcinoma: Amorphous, curvilinear or irregular calcification
12. Renal papillary necrosis
13. Acute cortical necrosis ('Tramline' calcification in renal cortex)
14. Oxalosis: Diffuse calcification
15. Hypercalcemia or hypercalciuria
16. Chronic glomerulonephritis (rare)
17. Rejection of renal transplant (cortical calcification).

Miscellaneous

CT scan in first 24 hours of stroke

Hemorrhage is seen within a few minutes as an increased attenuation. In middle cerebral infarct there is subtle loss of distinction between grey and white matter.

Ring enhancement lesions on computerized tomography scan

1. Cerebral abscesses
2. Tuberculoma: Ring enhancement seen with contrast media
3. Metastases with contrast media

Ventilator perfusion lung scan

Perfusion scan: Microaggregates of albumin labelled with technetium 99 m injected I.V. These microaggregates get trapped in pulmonary capillaries and their distribution is imaged by a gamma-camera. This reveals pulmonary perfusion.

Ventilation scan: Radioactive gases (Xenon 133 or Krypton 81m or Technetium 99m) are inhaled by the patient. The distribution of this radioactive gas is imaged by a gamma-camera. This indicates pulmonary ventilation.

Hazards of radiation

Skin: Pigmentation of skin due to melanocyte injury. Scarring may occur.

GI tract: Gut obstruction due to fibrosis. Fistula formation and rectal ulceration.

Bone marrow: (a) Mild-dose – Decrease in number of actively dividing cells. Number of erythroblasts exceeds myelocytes and megakaryocytes. (b) Moderate dose: Bone marrow becomes cellular and is replaced by fat. (c) Large dose: Aplastic anemia.

Bone: Necrosis and fractures

Ureters and bladder: Fibrosis of ureters due to damage to ureteric vessels. Fibrosis of bladder with subsequent contraction.

Female genitals: (a) Ovaries – pyknosis and degeneration of ovary and Graffian follicles. Follicular lining cells phagocytise ova. (b) Uterus: Necrosis and perforation.

Radiological features of hemolytic anemia.

Skull: Thickened diploe. 'Hair on end' appearance. Obliteration of paranasal sinus.

Bones: Thin cortex. Thickened and coarse trabeculae. Osteopenia. Widening of diaphysis and metaphysis. Ribs may be enlarged. Phalanges may appear rectangular with flattening of their concavities. H-shaped vertebrae in

sickle cell anemia. Changes due to infarction – Soft tissue swelling. Flattening and sclerosis at ends of humerus and femur. Periosteal reaction and periosteal new bone formation in shafts of long bones with foci of bony destruction.

Gallbladder: Gallstones on USG.

Mammography (radiological examination of the breast)

- Benign lesions: Well circumscribed and homogenous with surrounding fatty tissue.
- Carcinoma: Poorly defined margins with spiculated or irregular outline. Fine, stippled calcification in periductal region and soft tissue diagnostic.

26. SOME DRUGS WITH MULTIPLE INDICATIONS

ACE Inhibitors

1. Hypertension (essential).
2. Renovascular hypertension.
3. Hypertension in scleroderma.
4. Hypertension with diabetic nephropathy.
5. Hypertension with peripheral vascular disease.
6. Hypertension and hyperuricemia.
7. Refractory heart failure.
8. Cardioprotection after acute myocardial infarction.

Acetazolamide

- Altitude insomnia
- Ataxia
- Catamenial epilepsy
- Drug, toxin-induced epilepsy
- Glaucoma
- Hypokalaemic periodic paralysis
- Metabolic acidosis

Acyclovir

- Bell's palsy
- Cytomegalovirus
- E-B virus
- Encephalitis
- Genital herpes
- Herpes simplex
- Herpes zoster
- Meningitis
- Varicella

Aspirin

1. In atherosclerotic stroke
2. In coronary artery disease and myocardial infarction in primary prevention and revascularization procedures and secondary prevention in unstable angina
3. In Dressler syndrome
4. In fever
5. In headache
6. As analgesic
7. In rheumatic fever
8. In thrombocytopenia, reactive
9. In thrombotic thrombocytopenic purpura

Atropine

1. In advanced life support
2. In A-V block
3. In myocardial infarction
4. In overdose and poisoning from
   - β-adrenergic antagonists
   - Anticholinesterases
   - Calcium channel blockers
   - Organophosphates
5. In sinus bradycardia
6. In COPD (as Nebulizer).

Azathioprine

1. Myasthenia gravis
2. Dermatomyositis
3. Polymyositis
4. Wegener's granulomatosis
5. SLE

Benzodiazepines

1. Generalized anxiety disorders: use benzodiazepines for short-term relief and try to switch to non-pharmacological methods wherever long-term treatment is required.
2. Panic disorders and agoraphobia: alprazolam is the drug of choice.
3. Agitated depression: benzodiazepines are added to antidepressants for first 1–2 weeks or alternatively use an antidepressant with antianxiety effect, e.g. amitriptyline, dothiepin and doxepin.
4. Insomnia: benzodiazepines are used when insomnia is interfering with day-to-day routine. Short-term benzodiazepines (Nitrazepam, Flurazepam and Lorazepam) are preferred for short duration.

5. NREM sleep disorders like enuresis and somnambulism (diazepam reduces duration of stage 4 NREM sleep).
6. Nightmares (diazepam also reduces REM sleep duration).
7. Pre-medication in anaesthesia.
8. Anticonvulsant use: diazepam (I.V.) is the drug of choice for status epilepticus and alcoholic seizures.
9. To produce skeletal muscle relaxation in various surgical procedures.
10. Treatment of alcohol withdrawal syndrome.
11. Acute mania: clonazepam along with lithium controls manic symptoms without much side effects.
12. Antipsychotic induced akathisia.

Beta-blockers

1. Angina and secondary prevention of myocardial infarction.
2. Cardiac arrhythmias.
3. Systemic hypertension.
4. Hypertrophic obstructive cardiomyopathy.
5. Fallot's tetralogy.
6. Thyrotoxicosis.
7. Pheochromocytoma.
8. Schizophrenia.
9. Migraine (prophylaxis).
10. Subarachnoid haemorrhage.
11. Anxiety.
12. Essential tremor.
13. Drug and alcohol withdrawal syndromes.
14. Glaucoma.

Bisphosphonates

1. Paget's disease
2. Hypercalcemia
3. Osteoporosis
4. Bone pain
5. Osteogenesis imperfecta
6. Progressive diaphyseal dysplasia
7. Multiple myeloma

Botulism Toxin A

1. Blepharospasm and hemifacial spasms
2. Cervical dystonia
3. Spasmodic torticollis
4. Axillary hyperhidrosis
5. Palmoplantar hyperhidrosis
6. Hyperfunctional facial lines or wrinkles
7. Focal limb dystonia
8. Sialorrhoea
9. Anal fissures
10. Migraine
11. Meigs' syndrome
12. Essential tremor
13. Tardive syndrome
14. Tourette syndrome

Bromocriptine

1. Parkinson's disease.
2. Acromegaly.
3. Hyperprolactianemia – Prolactin secreting pituitary adenoma. Suppression of lactation.
4. Cyclic benign breast disease.
5. Premenstrual syndrome.
6. Neuroleptic malignant syndrome
7. Obesity in diabetes mellitus
8. Prolactin secreting tumors.

Calcium-channel Blockers

1. Angina.
2. Hypertension.
3. Hypertrophic cardiomyopathy.
4. Subarachnoid hemorrhage (Nimodipine).
5. Raynaud's phenomenon.
6. Systemic sclerosis.
7. Pulmonary hypertension.
8. Migraine prophylaxis.

Carbamazepine

1. Epileptic seizures.
2. Trigeminal neuralgia and other neuralgic pains.
3. Mood disorders (manic and depressive episodes).
4. Bipolar disorder
5. Diabetic neuropathy
6. Multiple sclerosis
7. Peripheral neuropathy
8. Sydenham's chorea
9. Stress disorders

Chloroquine

1. Malaria.
2. Hepatic amoebiasis.
3. Rheumatoid arthritis.

4. Lupus erythematosus, discoid and systemic.
5. Clonorchiasis.
6. Lepra reaction.
7. Porphyria

Colchicine

1. Alcoholic liver disease
2. Gout
3. Primary biliary cirrhosis
4. Amyloidosis
5. Familial Mediterranean fever
6. Behcet's syndrome
7. Myelofibrosis

Corticosteroids

1. *Allergic conditions*
   - Bronchial asthma
   - Allergic rhinitis
   - Contact dermatitis
   - Urticaria
   - Atopic dermatitis
   - Angioneurotic
   - Serum sickness
   - Oedema
2. *Cardiac disease*
   - Acute rheumatic fever
   - Heart block (1st degree)
3. *Dermatology*
   - Pemphigus Stevens-Johnson syndrome
   - Severe seborrhoeic
   - Pemphigoid dermatitis
   - Severe psoriasis
   - Mycosis fungoides
   - Herpetiformis
   - Bullous dermatitis
   - Lichen planus
4. *Endocrine disease*
   - Adrenocortical insufficiency
   - Congenital adrenal hyperplasia
   - Hashimoto's thyroiditis
   - Hypercalcemia of malignancy
5. *Gastrointestinal disease*
   - Inflammatory bowel disease
6. *Haematological disorders*
   - Immune haemolytic anemia, ITP
7. *Neoplastic diseases*
   - Acute lymphoblastic leukaemia
   - Lymphoma
8. *Ophthalmic disease*
   - Herpes zoster
   - Optic neuritis
   - Uveitis
   - Keratitis
   - Allergic
   - Conjunctivitis
9. *Respiratory diseases*
   - Sarcoidosis
   - Berylliosis
   - Fulminating tuberculosis
10. *Rheumatological diseases*
    - RA
    - Polymyositis
    - SLE
    - Psoriatic arthritis

Dapsone

1. Dermatitis herpetiformis
2. Leprosy
3. Pneumocystis jiroveci infection
4. Leishmaniasis
5. Malaria
6. Toxoplasmosis gondii

Diethylcarbamazine

1. Tropical eosinophilia.
2. Filariasis.
3. Loiasis
4. Onchocerciasis
5. Streptocerciasis

Doxorubicin

1. Follicular lymphoma
2. Hepatocellular carcinoma
3. Kaposi's sarcoma
4. Multiple myeloma
5. Salivary gland tumors
6. Thymoma
7. Zollinger-Ellison syndrome

Doxycycline

1. Acne rosacea
2. Acne vulgaris
3. Actinomycosis
4. Anthrax
5. Brucellosis
6. Cat scratch disease
7. Donovanosis
8. Endocarditis
9. Epidemic typhus
10. Gonococcal infection
11. Legionellosis
12. Lyme borreliosis
13. Lymphatic filariasis

14. Malaria
15. Meningitis
16. Onchocerciasis
17. Pneumonia
18. Psittacosis
19. Q fever
20. Rickettsial pox
21. Staphylococcal infection
22. Tularemia
23. Urinary tract infections

Erythropoietin

1. Anemia of kidney failure
2. Anemia of chronic disease, e.g. RA
3. Aplastic anemia (in combination with other human growth factors)
4. Anaemias of cancer (e.g. breast and colonic cancers, multiple myeloma, non-Hodgkin's lymphoma)
5. Myelodysplastic syndrome
6. HIV infection (Anemia due to zidovudine therapy)
7. Autologous blood transfusion (to boost normal erythropoietic response in preoperative settings to increase number of units of blood that can be safety removed and preserved for autologous transfusion in postoperative patients)
8. Other conditions
   - Anemia in premature infants with low EPO production
   - Poor response to iron therapy in nutritional anemia
   - Iron removal by phlebotomy
   - To reduce requirement of RBC transfusion following conditioning regimen during bone marrow transplantation.

Gammaglobulin (Intravenous)

I. ***Haematology***
Immune disorders
   - Idiopathic thrombocytopenic purpura
   - Post-transfusion purpura
   - Neonatal platelet alloimmunization
   - Neonatal thrombocytopenia following ITP in mother
   - Autoimmune neutropenia in children
   - Autoimmune haemolytic anaemia
   - Rhesus-isoimmunization in pregnancy
   - Red cell aplasia and pancytopenia
   - Thrombotic thrombocytopenic purpura and Haemolytic uremic syndrome
   - Coagulation inhibitors (e.g. acquired factor VIll deficiency)
   - Virus associated haemophagocytic syndrome
   - Guillain-Barre syndrome.

II. ***HIV-Infection*** – (a) HIV related thrombocytopenia. (b) CMV infection. (c) Children with HIV because of marked susceptibility to serious bacterial infections.

III. ***Bone marrow transplantation***

Glucagon

1. β-blocker overdose
2. Hypoglycemia
3. Cardiac inotropic for treatment of shock.

Granulocyte Maturation Colony Stimulating Factor

1. Transplant patients who exhibit early graft failure.
2. To mobilize progenitor cells for peripheral bloodstem cell (PBSC) for transplantation after myeloablative chemotherapy.
3. To shorten period of neutropenia and reduce mortality in patients receiving intense cancer chemotherapy.
4. To stimulate myelopoiesis in some patients with cyclic neutropenia, myelodysplasia, aplastic anemia or AIDS associated neutropenia.
5. Therapy for pulmonary alveolar proteinosis.

Growth Hormone

Indications:

1. GH deficient short stature in children.
2. Repeated hypoglycemia in GH deficient infants and children.
3. Turner's syndrome in early childhood.
4. Growth retardation in chronic kidney failure prior to kidney transplant.
5. Adults with GH deficiency following pituitary tumour surgery or irradiation or idiopathic hypopituitarism.
6. Strong evidence of protein catabolism, e.g. burns injury.

Possible indications:

a. Normal short children. In children the end points of GH therapy include achievement of discardable adult height or growth rate velocity of < 2.5 cm/year.

b. Short children with miscellaneous syndromes, e.g. skeletal dysplasias, spina bifida, Prader-Willi syndrome, Down syndrome, Russel Silver syndrome, Noonan syndrome.

c. Short children with X-linked Hypophosphatemic rickets.
d. Non-GH deficient adults, particularly beyond 6th decade. (Short duration to improve bone density and increase in lean body mass).
e. Catabolic states – Burns, extensive soft tissue injuries, cachexia (following major trauma, surgery), and septic shock.
f. AIDS – GH therapy for anabolic effects and potential effects of GH on immune system.
g. Infertility – GH facilitates ovulation induction in infertile women. GH therapy improves semen profile in patients with abnormalities of sperm maturation.
h. Osteoporosis – GH increases calcium and phosphate absorption from the gut by increasing 1,25 dihydroxy vitamin D production and by direct effect.
i. CHF – In patients. with dilated cardiomyopathy 14 IU/week increases myocardial mass, reduces LV dilatation and improves haemodynamics.
j. Tumour hypoglycemia – patients with non-islet cell tumours.

Haemopoietic Growth Factor

A. *Haematological malignancies*
   1. Therapy-induced myelosuppression
   2. AML –
      a. Treatment associated neutropenia
      b. Priming with colony stimulating factors
   3. High dose chemotherapy with rescue –Leukemias, lymphomas, multiple myeloma
   4. Role of other growth factors:
      a. Erythropoietin: Alleviating chemotherapy induced anaemia and decreasing transfusion requirements.
      b. Others: (i) Prophylactic use – When chemotherapy is expected to have febrile neutropenia equal to or greater than 40%. (ii) When previous chemotherapy has resulted in febrile neutropenia with life threatening infection. (iii) Use during neutropenia: In infections with high risk factors, e.g. pneumonia, hypotension, multiorgan dysfunction and fungal infections, use of colony stimulating factor along with antibiotics.
   5. Bone marrow transplantation
   6. Myelodysplastic syndromes

B. *Radiation mucositis*

Human Serum Albumin

1. Plasma volume replacement
2. Burns
3. Extracorporeal circulation during cardiac surgery
4. Nephrotic syndrome
5. Cirrhosis and ascites
6. Therapeutic plasma exchange
7. Neonatal hyperbilirubinaemia

Hyperbaric Oxygen

Acute conditions (where HBO therapy should be given earliest when compared to conventional treatment)

1. Non-healing ulcers, problem wounds, compromised skin grafts and flaps
2. Crush injury, compartment syndrome, and acute traumatic ischemia
3. Gas gangrene/clostridial infections
4. Necrotizing soft tissue infections (subcutaneous tissue, muscle, fascia)
5. Thermal burns
6. Exceptional blood loss (anaemia)
7. Intracranial abscess
8. Post-anoxic encephalopathy
9. Burns
10. Sudden deafness
11. Ocular ischemic pathology
12. Air or gas embolism*
13. Decompression sickness*
14. Carbon monoxide poisoning and smoke inhalation*

* Curative/primary line of treatment

Chronic conditions

1. Non-healing wounds/problem wounds (diabetic/venous, etc.)
2. Radiation tissue damage
3. Skin grafts and flaps (compromised)
4. Chronic osteomyelitis (refractory).

Immunoglobulin

1. Hepatitis A, B
2. Measles
3. Myasthenia gravis
4. Parvovirus B19 infection in HIV
5. Varicella zoster virus

6. Rabies
7. Tetanus
8. Thrombocytopenic purpura

Interferon Alpha

1. Hairy cell leukaemia
2. Chronic myeloid leukaemia
3. Multiple myeloma
4. Low grade lymphoma
5. Chronic lymphocytic leukaemia
6. Kaposi's sarcoma
7. Malignant melanoma
8. Others
   Recurrent glioma (along with tamoxifen)
   Neuroblastoma (combined with valproic acid).

Interleukin - 2

Infectious diseases

1. HIV infections and AIDS
2. Lepromatous leprosy
3. Disseminated cutaneous leishmaniasis
4. Hypogammaglobulinaemia
5. Chronic viral hepatitis
6. Human papilloma virus infections
7. Relapsing multiple sclerosis
8. Sezary syndrome
9. Essential mixed cryoglobulinaemia
10. Mastocytosis
11. Polycythemia vera

Malignancies

1. Anticancer gene therapy
2. Metastatic renal carcinoma
3. Metastatic melanoma
4. Other malignancies: Thymoma, acute myeloid leukaemia
5. Condyloma acuminatum (intralesional)
6. Carcinoid syndrome
7. Essential mixed cryoglobulinaemia
8. Kaposi's sarcoma
9. Mastocytosis
10. Polycythemia vera
11. Mycosis fungoides
12. Relapsed, remitting multiple sclerosis (INF-B)
13. May be protective in development of GVHD (IFN-r)

Ivermectin

1. Onchocerciasis
2. Lymphatic filariasis
3. Intestinal nematodes – Ascariasis, stronglyloidiasis, trichuriasis, enterobiasis.
4. Scabies
5. Head lice
6. Cutaneous larva migrans

Levamisole

1. Recurrent aphthous stomatitis
2. Recurrent herpes infections
3. Recurrent skin and respiratory infections
4. Rheumatoid arthritis
5. Chronic staphylococcal infections
6. Anthelmintic (ascariasis, hookworm, trichuris, strongyloidiasis)
7. Breast carcinoma.

Methotrexate

1. Gastric adenocarcinoma
2. Breast cancer
3. Inflammatory bowel disease
4. Multiple sclerosis
5. Myositis
6. Psoriasis, psoriatic arthritis
7. Reactive arthritis
8. Relapsing polychondritis
9. Rheumatoid arthritis
10. Vasculitis
11. SLE

Metronidazole/Tinidazole/Secnidazole

1. Amoebiasis.
2. Giardiasis.
3. Ulcerative gingivitis.
4. Trichomonas vaginalis (both sexes).
5. Anaerobic infections.
6. Brain abscess.
7. Clostridial associated colitis
8. Skin infections
9. *Helicobacter pylori* gastritis.
10. Subpleural empyema.
11. Rheumatoid arthritis.

Penicillamine

1. Rheumatoid arthritis
2. Wilson's disease
3. Systemic sclerosis
4. Primary biliary cirrhosis
5. Cystinuria
6. As chelating agent for heavy metal poisoning.

Rifampicin

1. Tuberculosis.
2. Leprosy.
3. Brucellosis – Children under 7 years of age and during pregnancy (in combination with Co-trimoxazole).
4. Prophylaxis for contacts of patient with meningococcal meningitis.
5. Prophylaxis of children under 4 years of age who have had close contact with a child with *H. influenzae* type B meningitis.
6. Eradication of nasal carriage in individuals with recurrent furunculosis (with cloxacillin).
7. Endocarditis due to Corynebacterium species, coxiella, chlamydia.
8. *L. pneumophilia* infection which has failed to respond to erythromycin, or in combination with erythromycin.
9. *Mycobacterium kansasii*
10. Staphylococcal infections
11. Streptococcus group A
12. *Streptococcus pneumoniae*
13. Chronic staphylococcal osteomyelitis (with nafcillin or vancomycin).

Rituximab

1. Autoimmune hemolytic anemia
2. B cell chronic lymphoid leukaemia/small lymphocytic lymphoma
3. HIV infection
4. Cerebellar degeneration
5. Cold agglutinin disease
6. Diffuse large B cell lymphoma
7. Epstein-Barr virus
8. Follicular lymphoma
9. Inflammatory myopathies
10. Leukaemia
11. Lymphoma
12. Monoclonal gammopathy of undetermined significance
13. RA
14. Thrombotic thrombocytopenic purpura
15. Waldenstrom's macroglobulinemia
16. Wegner's granulomatosis

Rivastigmine

1. Alzheimer's disease
2. Parkinson's disease

Sodium chromoglycate

1. Prevention of bronchial asthma.
2. Allergic rhinitis.
3. Ulcerative colitis.
4. Food allergies.

Statins

1. Lipid lowering therapy
2. Antiarrhythmic therapy
3. Peripheral arterial disease
4. Non-ischemic cardiomyopathy
5. Neuroinflammatory disorders: MS, Alzheimer's disease, ischemic stroke
6. Psychological well-being: Reduced risk of depression in patients with CAD
7. Cancer: Antitumor effects against melanoma, pancreatic carcinoma, glioma, neuroblastoma and lymphoma
8. Osteoporosis
9. Age-related maculopathy.

Thalidomide
(Used only when no alternatives)

1. Erythema nodosum leprosum
2. Major aphthae of mouth, oesophagus, genital, and anus (in isolation, as part of Behcet's disease, or in HIV infection)
3. Chronic graft versus host disease
4. Dermatological conditions – Discoid lupus erythematosus, prurigo nodularis, actinic prurigo, erythema multiforme, pyoderma gangrenosum
5. Inflammatory conditions – Rheumatoid arthritis, ulcerative colitis, post-herpetic neuralgia
6. Multiple myeloma.

Transfer Factor

1. Varicella-zoster prophylaxis in childhood leukaemia.
2. Wiskott-Aldrich syndrome.

3. Chronic mucocutaneous candidiasis (maintenance therapy).
4. Cutaneous leishmaniasis.
5. Lepromatous leprosy.

Vasopressin

1. Diabetes insipidus
2. Haemophilia
3. Hyponatremia
4. Uraemia and bleeding
5. Variceal bleeding
6. Von Willebrand's disease
7. Septic shock (by decreasing catecholamine requirement).

Verapamil

1. AV nodal re-entrant tachycardia
2. Angina pectoris
3. Aortic dissection
4. Hypertension
5. Hypertrophic cardiomyopathy
6. Steroid-resistant nephrotic syndrome
7. Insulinomas.

Plasmapheresis/Plasma Exchange

Established indications:

1. Hyperviscosity syndrome.
2. Goodpasture's syndrome. (Non-oliguric anti-GBM disease).
3. Myasthenia gravis (crisis or thymectomy).
4. Guillain-Barre syndrome.
5. Homozygous familial hypercholesterolemia.

Anecdotal indications:

1. Severe refractory collagen-vascular disease, e.g. SLE, RA.
2. Essential mixed cyroglobulinaemia.
3. Refractory thrombocytopenic purpura – Idiopathic ITP, thrombotic TTP, post-transfusion.

The **Dyslipidemia** of metabolic syndrome is characterized by elevated triglycerides (VLDL), low HDL and small dense LDL, a triad termed *atherogenic lipoprotein phenotype.*

Gastroenterology Liver and Biliary Diseases

Normal GI fluid volumes

- Food and drink 1500 ml
- Saliva 750 ml
- Gastricsecretion 1250 ml
- Biliary secretion 1000 ml
- Pancreatic secretion 2500 ml

Alcohol-induced recurrent abdominal pain:

1. Alcoholic hepatitis.
2. Alcoholic gastritis/peptic ulcer
3. Acute pancreatitis.
4. Others-Lead poisoning, Hodgkin's disease, acute intermittent (or variegate) porphyria.

Effects of Drugs on Teeth, Oral mucosa and Salivary glands

Discoloration of teeth	Chlorhexidine, tetracyclines, iron
Oral candidiasis	Broad spectrum antibiotics, corticosteroids (systemic and topical), cytotoxic drugs
Oral ulceration	Aspirin applied topically, penicillamine
Gingival hyperplasia	Phenytoin, calcium channel blockers (e.g. nifedipine, diltiazem), cyclosporin
Erythema multiforme	Sulphonamides, barbiturates, penicillin, carbarmazepine
Lichenoid reactions	Oral hypoglycemic agents, NSAIDs, beta-blockers, allopurinol, methyldopa
Mucosal pigmentation	Antimalarials (e.g. chloroquine), phenothiazines, oral contraceptives
Xerostomia (dry month)	Antihistamines, tricyclic anti-depressants, MAO inhibitors, diuretics, anti-cholinergic drugs, anti-parkinsonian agents (benzhexol, benztropine)
Salivary gland pain and swelling	Phenothiazines, anti-thyroid drugs, insulin

Recurrent (chronic) GI bleeding:

1. *Local lesions:* Angiodysplasia, hemangioma, hereditary hemorrhagic telangiectasia, diverticulitis (including Meckel's).
2. *Systemic causes:* Polycythemia vera, vasculitis (PAN, Henoch-Schonlein); Behçet's syndrome, amyloidosis, inherited collagenoses, pseudoxanthoma elasticum, type IV Ehlers-Danlos syndrome, Degos disease and miscellaneous—Peutz-Jegher's syn., Gardner's syn., blue rubber bleb naevus syn.

Chronic mesenteric ischemia. Causes:

- Atherosclerosis
- Fabry's disease
- Antiphospholipid antibody syndrome
- Behçet's disease
- Thromboangiitis obliterans
- Takayasu arteritis
- Crohn's disease
- External compression

Conditions associated with small intestinal bacterial overgrowth

- Reduced gastric acid
  - Pernicious anemia
  - Atrophic gastritis
  - Castric surgery
  - **Drugs:**
  - H_2 receptor antagonists
  - Proton pump inhibitors
- Structural abnormalities
  - Small bowel diverticula
  - Surgical anastomosis and diversions Strictures
  - Adhesions
  - Fistula (gastrocolic, coloenteric)
- Dysmotility syndromes
  - Diabetes
  - Scleroderma
  - Acute enteric infection
  - Intestinal pseudo-obstruction syndrome

Elevated serum CA-125 levels should not be relied upon to make a diagnosis of ovarian/peritoneal carcinoma in a case of ascites. CA-125 levels can be elevated in conditions like endometriosis, pelvic inflammatory disease and pleural and peritoneal effusion of many etiologies, such as CKF, cirrhosis, TB, CHF and many malignancies.

Double balloon enteroscopy (DBE) is a useful technique for small bowel diagnosis, for obscure GI bleed. It is a safe method for obtaining tissue for diagnosis, providing hemostasis, and carrying out polypectomy.

Cirrhosis with large liver

1. Alcoholic liver disease
2. Alcoholic hepatitis
3. Alcoholic cirrhosis
4. Postnecrotic cirrhosis with
   a. Superimposed viral hepatitis
   b. Superimposed alcoholic hepatitis
   c. Superimposed hepatocellular Ca
5. Budd-Chiari syndrome
6. Biliary cirrhosis

7. Cardiac cirrhosis
8. Metabolic liver disease
9. Wilson's disease
10. Hemochromatosis
11. Glycogen storage disease

Reduced drug dosage or frequency in liver disease

Analgesics: Pentazocin, dextropropoxyphene.

β-*blockers:* Propranolol, metoprolol, labetalol

Antidepressants: Imipramine, amitryptiline, desipramine, doxepin, haloperidol.

Sedatives: Chlormethiazole.

Anti-arrhythmics: Verapamil, diltiazem.

Non-alcoholic steatohepatitis (NASH) is a condition histologically similar to alcoholic liver disease but in which alcohol has no part and that is most commonly associated with obesity and/or type 2 diabetes. The condition can lead to cirrhosis and hepatocellular cancer.

NASH is now the most common cause of persistent elevation of liver enzymes (notably ALT) in patients in whom no other obvious cause can be found. Ultrasonography shows widespread fat in the liver.

Ascites

Classification of Ascites as per SAAG*

High gradient	Low gradient
(SAGG > 1.1 gm/dl)	(SAGG < 1.1 gm/dl)
Cirrhosis	Tubercular peritonitis
Alcoholic hepatitis	Peritonitis
Fulminant hepatic failure	Carcinomatosis
Portal vein thrombosis	Pancreatic ascites
Budd-Chiari syn.	Biliary ascites
Congestive heart failure	Serositis
Mixed ascites	Nephrotic syn.
Serum Ascites Albumin gradient*	
Serum albumin (gm/dl)—Ascitic fluid albumin (gm/dl)	

Ascites: Sudden worsening in stable cirrhosis:

1. Spontaneous bacterial peritonitis.
2. Budd-Chiari syndrome.
3. Hepatoma.
4. Acute deterioration of hepatocellular function (due to sepsis, alcoholic indulgence, gut bleeding).
5. Rupture of dilated abdominal lymphatics (chylous ascites).

- When the ascitic fluid contains more than 250 neutrophils/mm^3, diagnosis of spontaneous bacterial peritonitis is made
- Bloody ascitic fluid occurs in 2% of cirrhotic patients, one-third of whom have hepatocellular carcinoma
- Cirrhotic patients exhibit high concentration of interleukin-6 and tumor necrosis factor in ascites
- High levels of cytokines in ascitic fluid in spontaneous bacterial peritonitis might be related to complications in these patients, particularly impaired circulatory and kidney function
- TIPS should be used in patients who respond poorly to paracentesis and in those who require frequently repeated taps.

Diseases associated with primary biliary cirrhosis

Common (up to 80%)

- Sicca syndrome

Less common (about 20%)

- Thyroid disease. Arthralgia
- Raynaud's syndrome
- Sclerodactyly
- Fibrosing alveolitis

Uncommon (5%)

- CREST syndrome
- Addison's disease
- Coeliac disease
- Glomerulonephritis
- Vitiligo
- Renal tubular acidosis
- Myasthenia gravis
- Hypertrophic pulmonary osteoarthropathy

Liver disease in pregnancy

1. Liver dysfunction in hyperemesis gravidarum is generally mild and resolves as the vomiting settles
2. Obstetric cholestasis usually presents as pruritus of the extremities in the last trimester. Jaundice is uncommon, it may follow pruritus by a few weeks
3. HELLP syndrome. Defining features are:

- Hemolysis (microangiopathic)
- Elevated ALT and aspartate aminotansferase
- Low platelets (100,000 × 10^9/litre)

The syndrome occurs in the setting of pre-eclampsia, with wt. gain and oedema, hypertension and abdominal tenderness over the liver. Most cases occur in the third trimester. Early delivery is helpful though the condition may progress or even develop *de novo* postpartum, peaking at about 48 hours after delivery. In full-blown eclampsia, rupture of the liver with massive peritoneal hemorrhage can occur.

4. Acute fatty liver of pregnancy is most common in first and multiple pregnancies. Onset is in third trimester, with vomiting, upper abdominal pain, anorexia and malaise. Later, DIC, leucocytosis, hyperglycemia and hyperammonemia develop and progress to fulminant liver failure.

5. Ovarian hyperstimulation syndrome is caused by fertility treatment. Ascites may require drainage, and correction of hemoconcentration is vital.
6. Other liver diseases: (a) Gallstone formation is increased by pregnancy, particularly in association with obstetric cholestasis. (b) Budd-Chiari syndrome may be seen during pregnancy due to heightened thrombotic tendency. (c) Hepatitis E has a high mortality in pregnancy, for unexplained reasons.

Clinical and laboratory findings which raise suspicion of hepatocellular carcinoma

1. New abdominal pain or wt. loss
2. Hepatomegaly
3. Hepatic bruit
4. Acute hemoperitoneum
5. Blood-tinged ascitic fluid
6. Persistent fever
7. Sudden increase in serum alkaline phosphatase
8. Increasing ratio of aspartate aminotransferase to alkaline aminotranferase
9. Polycythemia or persistent leucocytosis
10. Hypoglycemia
11. Hypercalcemia
12. Hypercholesterolemia

Note: 9-12 are paraneoplastic syndromes associated with HCC.

Hepatic tumour-specific markers

α-*Jetoprotein* – Levels above 400 ng/ml are suggestive and above 1000 ng/ml are diagnostic of hepatocellular carcinoma or germ-cell tumour. High levels sometimes in chronic hepatitis, acute cirrhosis or during recovery from massive hepatic necrosis. Fucosylated a-fetoprotein measurements may help if a-fetoprotein levels are equivocal (20-1000 ng/ml) range.

Desgamma carboxyprothrombin (DCP) – Levels (normal 0.1 AU/ml) are increased in 60% of patients with hepatocellular carcinoma.

Consequences of sleep-related GER

Insomnia	Barret's esophagus
Sleep disturbance	Adenocarcinoma of esophagus
Impaired day time functioning	Recurrent pneumonia and aspiration
Impaired quality of life	Nocturnal asthma
Erosive esophagitis	Nocturnal laryngospasm

Groups at risk of opportunistic pneumonias

Dysphagia and oesophageal disease
Stricture Achalasia
Oesophageal pouch
Fistula
Hiatus hernia
Reflux

Eosinophilic ascites. Eosinophilic gastroenteritis. Patients with serosal variant of EGED present with eosinophilic ascites. It mainly affects children and young adults. EGED has three variants – (a) Mucosal disease – Abdominal pain, vomiting, diarrhea, protein-losing enteropathy. (b) Muscle layer disease – Bowel wall thickening, gastric and small bowel obstruction. (c) Serosal disease associated with eosinophilic ascites.

Chronic abdominal pain. Mesenteric ischemia should be suspected in elderly patients with chronic abdominal pain and in those with other risk factors.

Primary ciliary dyskinesia (PCD). Clinical features may be varied including distress in neonates, bronchiectasis, situs inversus, infertility, hydrocephalus singly or in various combinations. Exhaled NO may be used as a screening test with level of NO regulator. Ciliated epithelial cells obtained from inferior or middle turbinate using a sterile cytology brush may be studied for ciliary beat using digital high-speed video imaging when the dyskinetic cilia are seen lack the classical sideways recover sweep.

Respiratory System

Thoracic endometriosis is a rare condition where endometrial cells are seen in pleural lung. Common presentations are recurrent pneumothorax or hemothorax.

Terzidone is WHO categorized group IV anti-TB drug. It has an antibiotic effect against *M. tuberculosis* and also *M.avium* for treatment of tuberculosis. It is classified as a second line drug. Its mode of action is similar to cyclosporin. Dose: 15-20 mg/kg/day. It is to be used with caution in patient with psychiatric comorbidities and epilepsy. Advantages over cyclosporin – Adverse side-events lesser, better tolerated, does not produce hypotension. It has the advantage of usefulness in schizophrenics and alcoholics.

Device to detect drug-resistant TB in 2 hours. The device called gene expert is useful in early diagnosis. The expert WSB test has been found to accurately and quickly detect TB.

Factors predisposing to aspiration pneumonia

Altered consciousness	Neurological disorders
Drug overdose	Pseudobulbar palsy
Anaesthesia	Myasthenia gravis etc.
Epilepsy	Nasogastric tubes
Cerebrovascular accident	Severe dental and upper airways sepsis
Alcoholism	Terminal illness

Groups at risk of opportunistic pneumonias

Primary immunodeficiency	Secondary immunodeficiency
B-cell deficiency (agammaglobulinemia) T-cell deficiency (Di George syndrome)	HIV infection (AIDS) Leukemias and lymphomas Corticosteroid therapy (particularly following organ transplantation and the treatment of hematological malignancies) Malnutrition, general debility, uremia, liver failure, etc.

Fever and pulmonary infiltrates in immuno compromised patients

Infection
Pulmonary oedema
Pulmonary hemorrhage
Drug-induced pneumonitis
Radiation pneumonitis
Malignant infiltration (e.g. leukemia, Kaposi's sarcoma)
Pulmonary emboli
Non-specific pneumonitis

Differential diagnosis of pulmonary-renal syndrome

Disease	Vasculitis	Granulomata	Features
• Wegener's granulomatosis	Present	Present	See text
• Microscopic polyangiitis	Present	Absent	Primary small vessel vasculitis is the most common cause of pulmonary renal syndrome (about 56% of cases)
• Churg-Strauss syndrome	Present	Present	See text
• Goodpasture's disease	Present	Absent	Linear IgG deposition on glomerular basement membrane Antiglomerular antibody positive in patients with ANCA, treatment should be as for primary small vessel vasculitis; prognosis may be better then in those with antiglomerular basement membrane antibody alone
• Systemic lupus erythematosus	Present	Absent	Antinuclear factor and anti-dsDNA positive Low C3 and C4.
• Henoch-Schonlein purpura	Present	Absent	Lung involvement uncommon IgA deposition in vessel walls and mesangium
• Behçet's disease	Present	Absent	Diagnosed on clinical criteria Associated with recurrent oral and genital ulceration, eye lesions (including uveitis) and skin lesions; renal involvement usually mild
• Infection	Rarely present (e.g. SLE)	Absent	Pneumonia may be associated with acute tubular necrosis or interstitial nephritis (rarely) Subacute infective endocarditis may be associated with ANCA-negative pauci-immune glomerulonephritis Post-streptococcal glomerulonephritis Blood cultures, atypical serology and antistreptolysin-0 titer should be undertaken

Cardiovascular System

Rheumatic aortitis. RA, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disorder may all be associated with aortitis involving the ascending aorta. The inflammatory lesion may extend to sinus of Valsalva, mitral valve leaflets and adjacent myocardium. Clinical manifestations are AR, aneurysm, and involvement of cardiac conduction system.

Endomyocardial Fibrosis (EMF) is a variant of obliterative, restrictive cardiomyopathy. Endocardium of either or both ventricles is markedly thickened with involvement of underlying myocardium

Cardiovascular system

Rheumatic aortitis. RA, ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disorder may all be associated with aortitis involving the ascending aorta. The inflammatory lesion may extend to sinus of Valsalva, mitral valve leaflets and adjacent myocardium.Clinical manifestations are AR, aneurysm, and involvement of cardiac conduction system.

Endomyocardial Fibrosis (EMF) is a variant of obliterative, restrictive cardiomyopathy. Endocardium of either or both ventricles is markedly thickened with involvement of underlying myocardium.

Loeffler endocarditis is a rapidly progressive, aggressive disease affecting principally males and associated with intense thromboembolic phenomena.

Infective endocarditis caused by nutritionally variant streptococci (NVS) is associated with increased incidence of complications, both embolization and cardiac failure.

High-dose Statin therapy provides cardiovascular benefit beyond conventional (low to moderate dose) statin therapy in patients with acute coronary syndrome by substantially reducing not only LDL but also the level of atherogenic APO and oxidized LDL.

	Tetralogy of Fallot	Trilogy of Fallot
Onset of cyanosis	At birth or within a year	After few years
Squatting	Common	Rare
Facies	Not typical	Often moon face
'a' waves	Small or none	Usually large
RV heave	Absent	Present
Systolic nurmur	Rarely loud	Loud with thrill
X-ray chest	Oligaemic lung fields Good pulmonary bay Right sided aortic arch (25% cases) RV hypertrophy not marked	Oligaemic lung fields but no pulmonary bay No right-sided aortic arch RV hypertrophy ++
ECG	No RBBB	RBBB may be present
Echo	Small P pulmonale Shunt across VSD	Large P. pulmonale Shunt across ASD
Catheterization	Marked reduction of oxygen saturation in LV No giant 'a' waves Stenosis more often infundibular	Slight to moderate fall in oxygen saturation Giant 'a' waves Stenosis more often valvar

Romano – Ward syndrome is an AD inherited disorder with prolonged QT interval that predisposes to VT, torsades de pointes, syncopal attacks and sudden death.

Valsalva manoeuvre: It consists of forceful expiration of air against the closed glottis with the mouth shut and nose held closed.

Normal response: Initially a small rise in the arterial pressure which results from sudden emptying of the pulmonary bed into the left atrium. After 10 seconds, when the manoeuvre is halted, there is a sudden increase in RV and LV filling causing an overshoot in the BP which results in reflex bradycardia.

Abnormal response: Arterial pressure does not fall when the venous return to RA is arrested, and there is no change in pulse rate or pressure during and after the period of strain. This response is labelled 'square wave' response because it also occurs in addition to early heart failure, in patients with large left to right shunts, tight MS or AS, and large volume of blood in the lungs. Diabetic neuropathy, tabes dorsalis, and adrenergic neuron-blocking drugs can all give abnormal response.

Muller's manoeuvre: It is opposite of Valsalva and consists of forced inspiration against closed glottis, with the mouth shut and nose held closed. It results in decrease in intrathoracic pressure.

Myocardial perfusion scintigraphy: Scintigraphy is particularly advisable in patients who have a suboptimal dilation and should be performed 2 to 4 weeks post angioplasty when vascular reactivity has subsided. Patients with persistent ischemic defects after angioplasty are known to be at high risk for restenosis, whereas those without ischemia have a very low restenosis rate.

Reversible cardiomyopathy may be found with alcohol use, pregnancy, selenium deficiency, hypophosphatemia, hypocalcemia, thyrotoxicosis, cocaine use and chronic uncontrolled tachycardia.

Postural orthostatic tachycardia syn. (POTS). Also known as orthostatic intolerance, it is defined as long standing reproducible symptoms in adequate cerebral perfusion on assumption of upright posture with insignificant change in BP but significantly elevated heart rate in absence of medications, dehydration, prolonged bed rest, neuropathy, or substantial wt. loss. It is commonly a disorder of young women.

Holiday heart syndrome: The syndrome consists of paroxysms of arrhythmias occurring particularly after a holiday or weekend bout of drinking alcohol in a chronic alcoholic. It is commonly associated with alcoholic cardiomyopathy but can occur in absence of vious cardiac disease. The common arrhythmias are supraventricular tachycardias of which atrial fibrillation is the commonest.

Sudden cardiac death:

1. *Coronary artery disease*
   Acute ischemic events

Chronic ischemic heart disease
2. *Cardiomyopathies*
   Dilated Hypertrophic
3. *Valvular inflammation/infiltration,* e.g. AS, myocarditis, sarcoidosis, amyloidosis
4. *Uncommon , subtle, ill-defined lesions*, e.g. RV dysplasia, cardiac tumours
5. *Lesions of molecular structure,* e.g. congenital long QT syndrome
6. *Definable functional anomalies,* e.g. WPW syndrome, idiopathic VF

Causes of upper extremity DVT

I *Primary*
A. Traumatic
   - Effort thrombosis
   - Blood vessel injury

B. Increased distal venous pressure
   - Cervical ribs
   - Long transverse processes of cervical spine
   - Musculofascial bands of subclavius muscle and costoclavicular ligament
   - Clavicular or 1st rib anomalies

C. Hypercoagulable state
   - Antiphospholipid antibodies
   - Factor V Leiden
   - Antithrombin III deficiency
   - Protein C & S deficiency
   - Prothrombin gene mutation
   - Hyperhomocystinemia
   - Pregnancy and oral contraceptive use

II *Secondary*
A. Central venous catheters
B. Malignant disease
   - Lymphoma/Leukaemia
   - Pancreas cancer
   - Breast cancer
   - Chest disorders: lung, pleura and oesophagus
   - Gastrointestinal tract

C. Pacemakers
D. Intravenous Drug Abuse

III *Idiopathic may be associated with occult cancer*

Hematology

Aggressive natural killer (NK) cell leukemia affects younger patients who present with general poor condition, fever and disseminated disease and often die within a short time from systemic disease or complications such as multiorgan failure.

Reed-Sternberg cell is characteristic cell of Hodgkin's disease. It is a large cell with multilobulated nuclei and abundant cytoplasm and has been postulated to arise from the germinal central B cell population in most cases. An infiltrate of apparently normal lymphocytes, plasma cells and eosinophils surround the RS cell with various degrees of fibrosis.

Differential diagnosis of acquired aplastic anemia

	Examples	Differential features
Inherited	• Fanconi's anaemia	Chromosome fragility, dysmorphism, family history
Malignant	• Dyskeratosis congenita	Nail/skin changes, leukoplakia, X-linked, family history
	• Hypoplastic myelodysplastic syndrome	Blood cell morphology, cytogenetics
	• Acute leukaemia (presenting as aplastic anaemia)	Spontaneous remission followed by leukaemic relapse
Toxic	• Irradiation	History of exposure
	• Chemotherapy	
Antibody-mediated	• Autoimmune pancytopenia	Multiple auto antibodies

Acute reversible kidney failure is a complication of multiple myeloma – MM should be considered as a case of unexplained ARF in middle aged and elderly patients.

Prurigo nodularis in Hodgkin lymphoma. Pruritus and prurigo nodularis have been associated with the disease. Other neoplastic skin manifestations are eczema, mycosis fungoides and erythema nodosum.

Paraneoplastic syndromes are rare disorders triggered by an altered immune system response to a neoplasm. They are defined as clinical syndromes with non-metastatic systemic effects that accompany malignant disease. Causes - CML, myasthenia gravis, long-term treatment with 6-mercaptopurine.

Patients with hematological malignancies are of increased risk of fungal infections particularly by aspergillus, zygomycoses and may progress rapidly and by highly destructive to local tissues.

Evan's syndrome is an autoimmune disorder characterized by simultaneous or sequential development of Autoimmune hemolytic anemia and Idiopathic thrombocytopenic purpura and/or immune cytopenia in absence of any cause.

Dyskeratosis congenita is a rare progressive bone marrow disorder associated with triad of skin pigmentation, nail dystrophy and mucosal leukoplakia.

Non-infectious causes of peripheral eosinophilia

Atopy	Haematological	Vasculitis	Dermatological	Drug	Other
Asthma Eczema Hay fever	Hodgkin's and non-Hodgkin's lymphoma Chronic eosinophilic leukaemia Systemic mastocytosis Chronic myelomonocytic leukaemia Chronic myeloid leukaemia Acute myeloid leukaemia Myelodysplastic syndrome	Churg-Strauss syndrome Polyarteritis nodosa Wegener's granulomatosis Other connective tissue diseases and vasculitides	Immunobullous disorders: dermatitis herpetiformis and pemphigoid Atopic dermatitis	NSAIDs β-Lactam antibiotics Sulfa-containing antibiotics Tetracycline Acetylsalicylic acid Carbamazepine Colchicine Nitrofurantoin Dapsone Minocycline	Allergic bronchopulmonary aspergillosis Sarcoidosis Addison's disease Eosinophilic myocarditis Familial eosinophilic syndromes Heavy metal poisoning Idiopathic eosinophilic pneumonias

Severity of acquired aplastic anaemia

	Peripheral blood	Bone marrow
Very severe	• Neutrophils < 0.2×10^9/litre	• < 25% normal cellularity
	• Platelets < 20×10^9/litre	• Moderately hypocellular (< 30%
	• Reticulocytes < 20×10^9/litre	of remaining cells haemopoietic)
	• Transfusion-dependent	
Severe	• Neutrophils $0.2–0.5 \times 10^9$/litre	• As for very severe
	• Otherwise as for very severe	
Non-severe	• Neutrophils $0.5–1.5 \times 10^9$/litre	• Hypocellular
	• Platelets $20–100 \times 10^9$/litre	
	• Reticulocytes $20–60 \times 10^9$/litre	

Bone marrow changes in aplastic anaemia are often patchy, and the assessment of cellularity, even with a good trephine, may be difficult.

Combination of cyclosporin and menabol in treatment of aplastic anemia

Immunoglobulin IV in thrombotic thrombocytic purpura.

Endocrine

Hypothyroidism with persistent constipation may exacerbate hyperammonemic portosystemic encephalopathy in patients with well compensated liver disease.

Primary hyperparathyroidism myopathy is relatively less common girdle muscle disease which presents with exaggerated tendon reflexes and is completely reversible with surgery of parathyroid adenoma.

Pheochromocytoma. The triad of headache, palpitation and sweating in a patient with hypertension should arouse suspicion of pheochromocytoma.

Gynecomastia can occur physiologically in 3 phases of life – Neonatal period, puberty and old age. Maternal oestrogens are responsible for the first phase, reduction of endogenous testosterone synthesis for the latter two phases.

Mechanisms by which hyperinsulinemia contributes to hypertension.

- Vasodilatation
- Increased sympathetic nervous system activity directly and from vasodilatation
- Increased renal salt sensitivity, sodium retention
- Increased renal sodium/hydrogen exchange
- Lowered free fatty acids stimulating aldosterone secretion
- Vascular smooth muscle cell proliferation
- Atherosclerotic coronary vascular rigidity

DM. Initiating insulin therapy with insulin as part or switching over to basal insulin in patients with poor glycemic control leads to improvement in glucose control with no major hypoglycemia.

Drugs which are potentially hypoglycemic

Class of Drugs	Drug	Action
Oral antidiabetics	Sulphonylureas Glinides	• Insulin secretion
Anti-inflammatories	Aspirin Indomethacin	• Drug interactions by linkage with proteins
Antiarrhythmics	Acetaminophen Flecain Quinidine Disopyramide	• Decrease in insulin resistance • Insulin secretion
Antibiotics or	Sulphamethoxazole	• Insulin secretion
Antimicrobials	Pentamidine Tetracyclines	
Antihypertensives	Beta blockers ACE inhibitors	• Interaction with hepatic gluconeogenesis • Sensitivity to insulin
Hypolipidemics	Fibrates	• Sensitivity to insulin
Antidepressants	Fluoxetine	• Stimulation of beta cells

Non-Diabetic Renal Disease (NORD) in patients with type 2 DM

Clinical clues:

1. Short duration of diabetes.
2. Rapid loss of kidney function.
3. Heavy proteinuria with normal kidney function.
4. Significant kidney dysfunction with minimal/normal albuminuria.
5. Active urinary sediment
6. Absence of retinopathy.

Lipoatrophy at insulin injection site is likely to be an immunological phenomenon as postulated that tissue necrosis factor α(TNF-α), which in turn inhibits the adipocyte and consequently resulting in lipoatrophy.

Common causes of ectopic ACTH syndrome

1. Ca lung (esp. small cell)
2. Carcinoid tumour of thymus
3. Medullary Ca of thyroid
4. Ca of colon
5. Pheochromocytoma

Lactic acidosis

I. Type A: any cause of severe tissue hypoxia.
II. Type B:
   1. 'Idiopathic'. Onset in elderly diabetics.
   2. Alcohol abuse and/or liver disease.
   3. Uremia.
   4. Leukemias (some), myeloproliferative disorders.
   5. Diabetes mellitus: Metformin, ketoacidosis.

Euthyroid hyperthyroxinemia is a condition in which thyroid hormone levels T4 and or T3 are elevated in the absence of thyrotoxicosis. It can occur in familial disalbuminemic hyperthyroidism (FDH), familial or acquired excess of transthyretin and drugs like propranolol and amiodarone. Also in states of resistance to thyroid hormone.

Causes of abnormal serum TSH concentrations, TSH below normal

- Primary hyperthyroidism
- Pituitary/ hypothalamic disease
- Prolonged thyrotrophic cell suppression after hyperthyroidism
- Old age
- **Drugs:** Glucocorticoids, dopamine
- Problems with T4 treatment e.g. overdosage, altered GI absorption, altered T4 clearance because of drugs
- Severe systemic illness (Sick euthyroid state)

TSH above normal

- Primary hypothyroidism
- Pituitary thyrotroph adenoma, pituitary resistance to thyroid hormone
- Thyrotoxicosis from rapid correction of severe hypothyroidism with parenteral T4
- Old age
- Drugs: e.g. amiodarone
- Problems with T4 treatment
- Recovering phase after severe systemic illness

Renal Disorders

- Psoriatic nephropathy—Mesangioproliferative GN with IgA deposits in RA, amyloidosis and membranous nephropathy are relatively common. Drug-related nephropathy can be due to high dosage of NSAIDs in psoriatic arthropathy.

In Fabry's disease, an inborn error of glycophospholipid metabolism, urine microscopy shows typical "mulberry cells".

Uremia — Cardiovascular risk factors

Uremic vasculopathy	Uremic cardiomyopathy
• Smoking	• Hypertension
• DM	• Anemia
• Hypertension	• Volume overload
• Dyslipidemia	• DM
• Hyperhomocysteinemia	• A-V fistula
• Increased oxidative stress	
• Elevated calcium phosphate	
• Inflammation	

Systemic disease in which GN may be a feature

- Connective tissue disease, particularly SLE
- Systemic vasculitis
- Infective endocarditis
- Other infections – Methicillin resistant Staph. aureus, malaria, hepatitis B virus, HIV
- Drug reactions – NSAIDs, gold, penicillamine
- Carcinoma, lymphoma, myeloma

Tubulointerstitial disorders

Acute tubulointerstitial disorders

- Acute interstitial nephritis
- Acute tubular necrosis
- Acute urate nephropathy (and other cryst al nephropathies)

Chronic tubulointerstitial disorders

- Chronic interstitial nephritis
- Reflux nephropathy
- Analgesic nephropathy
- Toxic nephropathies (uric acid, heavy metals)
- Radiation nephritis
- Balkan nephropathy
- Nephronophthisis
- Medullary sponge kidney

Primary tubular disorders

- Fanconi's syndrome
- Renal glycosuria
- Aminoacidurias (including cystinuria)
- Familial X-linked hypophosphatemic rickets
- Renal tubular acidosis
- Gittleman's and Barter's syndromes
- Nephrogenic diabetes insipidus

Systemic disease affecting the tubulointerstitium

- Myeloma
- Sarcoidosis
- Sjogren's syndrome
- Systemic lupus erythematosus
- Sickle cell anemia
- Hyperoxaluria
- Cystinosis

Interpreting creatinine and urea

Creatinine	Urea
Raised	*Raised*
• Large muscle bulk	• Reduced glomerular filtration rate (including dehydration)
• Acute rhabdomyolysis	• Gastrointestinal bleeding
• Reduced tubular secretion (trimethoprim, cimetidine, potassium-sparing diuretics, probenecid, triamterene)	• Corticosteroids/tetracycline
	• Catabolic state
	• High-protein diet
Reduced	*Reduced*
• Small muscle mass • Pregnancy	• Liver disease
• Raised antidiuretic hormone	• Starvation/anabolic state
	• Pregnancy
	• Raised antidiuretic hormone

Causes of rapidly progressive glomerulonephritis

- Antineutrophil cytoplasm antibody-associated vasculitis (including isolated antineutrophil cytoplasm antibody-associated glomerulonephritis)
- Antiglomerular basement disease (Goodpasture's disease)
- Lupus nephritis
- Crescentic phase of primary glomerulonephritis (e.g. IgA nephropathy)
- Post-infectious glomerulonephritis
- Cryoglobulinemic glomerulonephritis

Clinical features that may be present when renal dysfunction is part of a systemic disease

Diabetic microvascular disease

- Diabetic nephropathy

Evidence of an underlying infection

- Acute infection with renal involvement (e.g. *Leptospira*, hantavirus)
- Chronic infection with associated glomerulonephritis (e.g. hepatitis B/C, HIV, *Filaria*, *Schistosoma mansoni*)
- Infection followed by post-infectious glomerulonephritis (e.g. *Streptococcus*)

Multi-organ inflammation

- Systemic lupus erythematous with glomerulonephritis
- Antineutrophil cytoplasm antibody-associated vasculitis with glomerulonephritis
- Sarcoidosis with interstitial nephritis

Rashes, fever and joint pains caused by allergy

- Drug-induced acute interstitial nephritis

Evidence of underlying malignancy

- Paraneoplastic glomerulonephritis
- Urinary tract obstruction
- Renal failure caused by hypercalcemia
- Myeloma with cast nephropathy

Features of generalized vascular disease

- Renal artery stenosis or occlusion
- Renal atheroemboli

Organomegaly and organ dysfunction from infiltrative disease

- Amyloidosis

Neurological abnormalities

- Neuropathic bladder with infection, stone or renal failure

Diagnostic definition of normo-, micro-and macroalbuminuria

Condition albumin excretion rate	*24-h urinary albumin excretion rate*	*Overnight urinary albumin excretion rate*	Albumin: **creatinine ratio***
Macroalbuminuria (overt nephropathy)	> 300 mg/day	> 200 μg/min	> 25 mg/mmol
Microalbuminuria	30-300 mg/day	20-200 μg/min	2.5-25 mg/mmol (for men) 3.5-25 mg mmol (for women)
Normoalbuminuria	< 30 mg/day	< 20 μg/min	< 2.5 mg/mmol (for men) < 3.5 mg/mmol (for women)

Tropical Infections

Abdominal Pain in Falciparum Malaria

Causes

- Acalculous cholecystitis
- Splenic rupture
- Splenic infarction
- Splenic torsion
- Hepatitis, hepatomegaly
- Acute pancreatitis

Plasmodium vivax is known to be benign nature but now life-threatening complications, such as ARDS, have been known to occur. The non-sequestration complications are anemia and thrombocytopenia. Severe manifestations include cerebral malaria, hepatic and renal dysfunction, ARDS, severe anemia, pulmonary oedema and hemoglobinuria. The rapid blood test is negative for falciparum malaria but positive for parasite malarial antigen.

Anemia, the mot common complications in malaria is due to accelerated RBC removal by the spleen, obligatory RBC destruction of parasite schizogony and ineffective hemopoiesis. A proportion of patients develop immune hemolytic anemia due to multifactorial factors, e.g. antibodies directed to parasite antigens sticking to red cells, immune complex deposition leading to hemolysis due to parasite antigen or drug antibody complex, etc.

Malaria due to co-existent P. falciparum and P. vivax infection in areas where both species co-exists. In mixed infection, P. vivax malaria has a protective effect against the severity of falciparum malaria.

Tetany in malaria. Alteration of calcium phosphate and magnesium metabolism can occur in malaria. Also quinine should be used cautiously in patients with severe malaria associated with hypocalcemic and prolonged QT interval.

Leptospirosis – Renal manifestations include oliguric renal failure due to acute tubular necrosis or tubulointerstitial damage leading to non-oliguric kidney failure, renal potassium wasting and hypokalemia.

Hemorrhagic complications of falciparum malaria: SAH, cerebral hemorrhage, bilateral subdural hematoma.

Polymerase chain reaction (PCR) by DNA amplification has 100% specificity and sensitivity for diagnosis of leptospiral infection.

Crimean congo hemorrhagic fever (CCHF) is caused by a virus. Humans get the infection by bite of an infected trick

or contact with infected blood of animals. It can also be transmitted from an infected human to another by contact with infectious blood or body fluids. *Cl.Fs.*–1. Prehemorrhagic phase – Sudden onset of fever, chills, severe myalgia, arthralgia, rash, photophobia. 2. In severe cases 3-6 days after onset of symptoms, hemorrhagic manifestations ranging from petechiae to ecchymosis, red eyes, hematemesis, hematuria. Patients can develop hypovolemic state, DIC, prerenal failure and multiorgan dysfunction syndrome *Lab diagnosis* - ELISA and PCR. Tr. Supportive. Anti-viral agent Ribavirin.

Diseases of Children

Neonatal critical care

Persistent pulmonary hypertension (PPHN) is basically a failed transition of fetal circulation to neonatal circulation.

Pathophysiology: Normal cardiorespiratory adaptations at birth are aeration of lungs, fall in pulmonary vascular resistance, closure of various fetal shunts, i.e. patent foramen ovale, ductus venosus and arteriosus. Alterations in this normal process leads to PPHN.

Pathological mechanisms leading to PPHN in various disease processes:

- Maladaptation of pulmonary vessels (perinatal asphyxia, meconium aspiration syndrome)
- Maldevelopment of pulmonary vessels (PPH)
- Underdevelopment of pulmonary vasculature (congenital diaphragmatic hernia)
- Structural/functional obstruction to pulmonary blood flow

Clinical features

- Cyanosis inspite of high supplemental O_2
- Tachypnoea 80-100/min
- Minimal signs on auscultation
- Mild tachycardia
- Loud P_2
- Pre and post-ductal O_2 gradient (-20 mmHg)
- Hypotension
- Hyporexia and hyperventilation test to differentiate it from cyanotic heart disease

Diagnosis: 2D echo - Structurally normal heart with supra-systemic PA pressures, right to left shunting at level of PFO and PDA. Dilated RV, TR.

Management:

1. Restore functional residual capacity of the lung using conventional or high frequency oscillatory ventilation (HTOV), and optimum PEEP.
2. Reduce peripheral vascular resistance (PVR). Maintain oxygenation > 80 mmHg. Nitric oxide is a selective pulmonary vasodilator. Other adjuvant therapies include avoiding hypercapnia, maintaining pH in range of 7.4-7.5, optimal sedation and muscle relaxation. Inhaled nitrous oxide (iNO) decreases PVR and extrapulmonary venoarterial shunting. It is contraindicated in severe IVH, platelets < 50,000 and irreversible pulmonary pathology.

Cold blanket for asphyxial neonates

Hypothermia arrests the extent of brain damage. The neonate's body temperature is lowered by a couple of degrees from the normal 37°C for 72 hours by using the blanket. The baby's temperature is then gradually raised to normal. The cold environment stops the damaging brain activity - like release of excitatory aminoacids that results in the newborn not crying in the first place.

Excessive crying in a baby

1. Hunger
2. Heat
3. Mosquito bites
4. Wet clothes
5. Blocked or stuffy nose
6. Infantile colic, e.g. from windiness
7. Pain anywhere in the body, e.g. earache
8. Restlessness at night, e.g. from darkness
9. Serious illness, e.g. raised intracranial pressure or brain damage.

Persistent crying in babies. Excessive crying is defined medically as crying that lasts atleast 3 hours a day, for 3 days a week, for atleast 3 weeks.

Nature of the crying: Babies cry for a variety of reasons, including hunger and thirst, being hot or cold, wanting attention, tiredness, discomfort and pain. The pattern of crying may indicate the problem, e.g. infantile colic (excessive crying in an otherwise healthy baby may manifest as long bouts of crying in the early evening).

Other symptoms: Difficulty in feeding may be due to a blocked nose, vomiting may indicate a GI problem, excessive straining may be due to constipation, and eczema suggests discomfort from itching.

Feeding: An underlying cause may be overfeeding or premature weaning. The baby may be inadvertently swallowing air, particularly at the end of a bottle feed.

Psychiatry

Drugs causing confusion in elderly:

1. Digoxin (also fatigue, euphoria).
2. Propranolol (also nightmares, insomnia).
3. Methyldopa.
4. Indomethacin (also vertigo, headache).
5. Cimetidine (esp. if renal or hepatic insufficiency).
6. Amantadine, L-dopa (esp. if used with anticholinergics).
7. Sedative-hypnotics, tricyclics, phenothiazines, alcohol.

Tardive dyskinesia:

Clinical features:

1. Orofacial dyskinesia.
   a. 'Fly-catcher' tongue.
   b. 'Bon-Bon' sign.
   c. Rumination, pouting.
2. Glottal dyskinesia - grunting.
3. Blepharospasm, increased blink frequency.
4. Torticollis.
5. Upper limbs.
   a. 'Piano-playing' fingers.
   b. Choreiform or ballistic movements.
   c. Shoulder shrugging.
6. Lower limbs.
   Writhing of lower legs

Obsessive-compulsive disorder. Non-psychiatrists are likely to see patients with OCD:

Professional	*Reason for consultation*
Family physician	Depression, anxiety
Dermatologist	Chopped hands, eczema, trichotilomania
Cosmetic surgeon	Concerns about appearance (body dysmorphic disorder)
Oncologist	Fear of cancer
Genitourinary specialist	Fear of HIV
Neurologist	OCD associated with Tourette's syndrome
Obstetrician	OCD during pregnancy or puerperium
Gynecologist	Vaginal discomfort from douching

Types of Munchausen's syndrome

Abdominal: Patients travel to various hospitals undergoing repeated operations, only to discharge themselves against advice (even with wounds still healing and I.V. drips in place).

Bleeding: Characterized by bleeding symptoms anticoagulant subtype, anemia subtype, pretended bleeding subtype.

Neurological: Unusual yet often convincing fits, spells, faints and anaesthesias.

Miscellaneous: Pyrexia. Dermatological. Endocrine. Munchhausen's syndrome by proxy: A form of child abuse in which a parent or carer feigns illness in a child.

Distinguishing delirium from dementia

	Delirium	Dementia
Onset	Acute or subacute	Insidious
Course	Fluctuating, usually revolves over days to weeks	Progressive
Conscious level	Often impaired, can fluctuate rapidly	Clear until later stages
Cognitive defects	Poor short term memory, poor attention span	Poor short term memory, attention less affected until severe
Hallucinations	Common, especially visual	Often absent
Delusions	Fleeting, non-systematised	Often absent
Psychomotor activity	Increased, reduced, or unpredictable	Can be normal

Autism: Three areas of impairment that characterize autism:

1. Social impairment
   Lack of social interest
   Lack of eye contact and gesture
   Poor peer relationship
2. Repetitive and routinized behaviour
   Stereotype
   Reference for routine
   Unusual preoccupation

3. Communications of an impairment
   Echolalia or non-communicative speech
   Language delay
   Stereotyped or repetitive speech

Postpartum psychosis: Presents with severe depression, mania, high suicidal drive, schizophrenia symptoms, persistent crying, lack of appetite, self and harm to within three months of delivery.

Voluntary and smooth muscle and skeletal disorders caused by alcohol misuse.

- Proximal metabolic myopathy (principally affecting type II).
- Neuromyopathy secondary to minor motor nerve damage
- Atrophy of smooth muscle of GI tract leading to motility disorders
- Osteopenia
- Gout
- Avascular necrosis (e.g. femoral head)
- Fractures - Malunion

Common differential diagnosis of depressive illness

Other psychiatric disorders	Alcohol misuse
	Amphetamine (and derivatives) misuse and withdrawal
	Borderline personality disorder
	Dementia
	Delirium
	Schizophrenia Normal and pathological grief
Organic (secondary) affective illness	Cushing's syndrome
	Thyroid disease (sometimes depression persists even after treatment)
	Hyperparathyroidism
	Corticosteroid treatment
	Brain tumor (rarely without other neurological signs)

Alice in Wonderland syndrome (Todd's syn.) is a type of psychiatric affection in which the individual has a disturbed assessment of self and suffers from fast forwarding of intrapsychic time. This may be encountered in some cases of migraine and of epilepsy.

Poisoning

Barium carbonate: Most cases of acute toxicity occur due to ingestion of barium carbonate (mostly suicidal), food contaminated by or carelessness in' handling of rat poison'. *Cl. Fs.* Abdominal pain, nausea, vomiting, flaccid paraplegia and respiratory paralysis which can develop within a few hours. Hypertension and cardiac arrhythmia. CNS - Myalgias, anxiety, headache, confusion and seizures. Hypokalemia occurs as a result of redistribution of body potassium. *Tr.* Gastric lavage, administration of sodium sulphate. IV potassium (upto 400 mEq).

Acute organophosphorus poisoning. Phases of neurological involvement:

I. Acute paralysis secondary to continued depolarization at the neuromuscular junction.
II. Intermediate syndrome develops 24 to 96 hours after resolution of initial phase, characterized by weakness of proximal muscles, cranial nerve palsies, and may require mechanical ventilation. Extrapyramidal symptoms — Dystonia, cogwheel rigidity and Parkinsonian facies.
III. Organophosphorus delayed polyneuropathy (OPIDP) occurs 2 to 3 weeks after exposure. Chronic OP induced neuropsychiatric disorders have also been reported.

Neurology

Transient Ischaemic Attacks. In the new definition of TIA, emphasis is laid on the fact that MRI must not show evidence of acute ischaemia, irrespective of the time period of recovery.

Temporal arteritis

- If ESR is normal, but CPR is high temporal arteritis should be suspected.
- MRI of temporal vessel. Ensure that skipped areas are not biopsied resulting in false negative biopsy.

Painful ophthalmoplegia

Common causes:
Herpes zoster
Intracranial aneurysm
Diabetes mellitus
Paranasal mucocele
Parasellar neoplasm
Carotid cavernous fistula
Tolosa-Hunt syn.
Ophthalmoplegic migraine
Arteritis
Ophthalmic Grave's disease
Congenital myopathy (myotubular variety)

Migraine: Sublingual Piroxicam 40 mg in migraine without aura has significant analgesic effect in acute management with excellent tolerability.

SAH: The two most common sites are proximal portion of anterior communicating artery and at the origin of

the posterior communicating artery from the stem of the internal carotid.

Sturge Weber syndrome is characterized by cutaneous angioma (portwine stain) typically involving the ophthalmic division of trigeminal nerve and an ipsilateral brain angioma with gyral calcification in parieto-occipital lobe. Principal neurological manifestations are epileptic seizures and focal neurological deficiency. Some patients may present with repeated episodes of facial weakness similar to TIAs.

Tension pneumocephalus is the term used to describe trapping of air intracranially. Usually, it occurs in patient whose brain dose not expand after removal of subdural hematoma. Simple procedure like burr hole and air drainage can be life saving.

Pisa syndrome refers to axial dystonia with severe tonic lateral flexion of the trunk. Disproportionate anticollis often seen as chin on chest, whereas rest of the body is normal.

Disorder of voltage-gated ion channels are responsible for a group of neurological and muscular diseases now called channelopathies. They are characterized by increased or decreased excitability of nerve or muscle.

Causes of acute facial palsy which are not idiopathic

- Suppurative otitis media
- Head injury (onset may be delayed by a few days)
- Herpes zoster
- G-B syndrome - Facial palsy may be an early predominant feature
- Sarcoidosis may present with isolated facial palsy
- Multiple sclerosis
- Lyme disease
- HN infection - Lymphadenopathy

Neurodegeneration with brain iron accumulation (NBIA) is characterized by progressive extrapyramidal degeneration presenting as a spectrum of cervical dystonia, dysarthria. MR brain is suggestive of characteristic 'eye of the tiger' appearance.

Reflex sympathetic dystrophy following pacemaker insertion an RSDS (Sudeck's atrophy) usually follows minor trauma or surgery or may occur spontaneously. The syndrome begins with spontaneous pain associated with vasomotor and sudomotor disturbances.

Clinical FMR: The patient is given specific task to perform (motor, visual, language, etc.) while MR sequences are able to detect increased O_2 delivery and blood flow to the areas of the brain that are responsible for those specific tasks are shown in color on the MRI images, e.g. if the patient is asked to do a right finger tap, then the functional area for the right hand in left cerebral hemisphere is seen as an activation.

Demyelinating diseases

CNS

- MS or its variant
- Transverse myelitis
- Devic's disease
- Acute disseminated encephalopathy
- Optic neuritis

Peripheral nerves

- G-B syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Anti-MAG (myelin associated glycoprotein) peripheral neuropathy

Panthothenate-kinase neurodegeneration (PKAN) with iron accumulation is characterized by progressive extrapyramidal dysfunctional and associated features like corticospinal involvement, intellectual impairment, retinitis pigmentosa, optic atrophy and seizure and 'eye of tiger' appearance on neuroimaging.

Parkinson's disease and Huntington's chorea

	Parkinsons disease	*Huntington's chorea*
Site of neuronal loss	Substantia nigra	Caudate nucleus
Neurotransmitter loss	Dopamine	Acetylcholine (and GABA)
Excess of	Acetylcholine	Dopamine
Levodopa therapy	Improvement	Exacerbation of chorea
Phenothiazine	Exacerbation	Improvement of chorea

Pathological classification of syringomyelia:

Type I: With obstruction of foramen magnum and dilatation of central canal:

a. With type I Chiari malformation.
b. With other obstructive lesions of foramen magnum

Type II: Without obstruction of foramen magnum (idiopathic).

Type III: With associated disease of spinal cord—tumors, arachnoiditis, traumatic myelopathy.

Type IV: Pure hydromyelia with or without hydrocephalus.

Bladder involvement is late in syringomyelia because lesions is lateral.

Nonmotor symptoms of Parkinosn's disease

1. **Neuropsychiatric symptoms**
   Depression, apathy, anhedonia, anxiety, panic attacks, attention deficit.
   Hallucinations, illusions, delusions (could be drug induced), obsessional behaviour.
   Dementia, confusion, delirium (could be drug induced).
2. **Sleep disorders**
   Restless legs and periodic limb movements, REM sleep behaviour disorder (RBD).
   Insomnia, excessive daytime somnolence.
   Vivid dreaming, sleep disordered breathing.
3. **Autonomic symptoms**
   Bladder disturbances: Urgency, nocturia, frequency.
   Sexual dysfunction: Hypersexuality (likely to be drug induced), erectile dysfunction.
   Abnormalities of sweating, orthostatic hypotension, dry eyes (xerophthalmia), dry mouth.
4. **Gastrointestinal symptoms**
   Dribbling of saliva (sialorrhoea).
   Delayed gastric emptying, ageusia, dysphagia, choking, reflux.
   Vomiting/nausea (usually drug related).
   Constipation/unsatisfactory voiding of bowel/faecal incontinence.
5. **Sensory symptoms**
   Pain/paraesthesia, olfactory disturbance (hyposomnia).
6. **Other symptoms**
   Fatigue, diplopia, blurred vision, seborrhoea.
   Weight loss, weight gain (possibly drug induced).

Parkinsonian tremor

Parkinsonian tremor	Essential tremor
Tremor faster	Tremor slower
At rest	Non-resting
Usually unilateral	Usually bilateral
Affects hands and legs	Affects hands, head and larynx
Starts in later life	Often present from childhood
Rapidly progressive	Slowly progressive
Reduced by ingestion of levodopa	Reduced by ingestion of alcohol
Signs of Parkinson's disease	No evidence of parkinsonism

Mitochondrial medicine

Mitochondrial diseases are extremely heterogeneous multisystem disorders predominantly affecting tissues or organs with high oxygen consumption like skeletal muscles, brain, endocrine glands, myocardium, etc.

Mitochondrial diseases

Neuromuscular system: Facial dysmorphism, mental retardation, dementia, impaired visual acuity, visual field, dry mouth, reduced gag reflex, exaggerated masseter reflex, gaze paresis, ophthalmoparesis, weakness, wasting, hypotonia, reduced deep tendon reflexes, long tract signs, fasciculation, myoclonus, cogwheel rigidity, dystonia, ataxia, brady/dysdiadochokinesia, sensory and gait disturbance.

Eye: Pigmentary retinopathy, optic atrophy, squint, cataract and glaucoma.

Endocrine system: Short stature, developmental delay, polyphagia, failure to thrive, hypopituitarism, diabetes mellitus, diabetes insipidus, hypoglycemia, thyroid and parathyroid dysfunction, amenorrhoea, hypogonadism, delayed puberty.

Gastrointestinal: Paraodontosis, dysphagia, gastrointestinal dysmotility, pseudo obstruction, recurrent vomiting, hepatopathy (acute liver failure), recurrent pancreatitis, villus atrophy, malabsorption, diarrhea, weight loss, anorexia.

Kidneys: Renal cysts, tubulopathy, Toni-Debre-Fanconi syndrome.

Blood: Anemia, leucopenia, thrombocytopenia, eosinophilia.

Congenital crocodile tears with congenital cranial dysinnervation syndrome. Lacrimation occurs while taking food. There is limitation of convergence, with narrowing of palpebral fissure. The likely cause is a defect in normal developmental cells forming abducens nucleus and superior lacrimal nucleus in brain stem.

Autonomic dysfunction

Clinical manifestations: of primary autonomic failure:

CVS	Postural hypotension
Urinary bladder	Frequency, urgency, incontinence, retention
Large bowel	Constipation, occasionally diarrhoea
Genital tract	Impotence in males
Sweat glands	Anhidrosis
RS	Stridor, respiratory gasps, apnoeic periods
Pupils	Anisocoria, Homer's syndrome
Other neurological defects	Parkinsonism, cerebellar and pyramidal signs

Moyamoya disease

It is progressive veno-occlusive disease of unknown cause involving arteries of the Circle of Willis. It presents as

ischemic stroke in children and intracranial hemorrhage in adults. It is associated with renal artery stenosis and renovascular hypertension in some.

Neurological conditions with a psychiatric presentation

1. Degenerative disorder, e.g. dementia
2. Head injury
3. Stroke
4. Epilepsy and non-epileptic fits
5. Parkinson's disease
6. Intracranial tumors
7. Intracranial infections
8. Nutritional, toxic or endocrine disorders.

Diseases causing fever with involvement of the CNS

Leptospirosis
Malaria
Scrub typhus
Typhoid Rabies
Arboviral encephalitis
Japanese encephalitis
Tick-borne encephalitis
Dengue
East African trypanosomiasis
Acute human immunodeficiency virus infection

Dermatology

Skin conditions of the male genitalia

Prominent sebaceous glands: Tyson's glands, sebaceous hyperplasia and ectopic sebaceous glands are common normal variants of skin of scrotal sac and penile shaft.

Erythroplasia Queyrat is sqamous cell carcinoma of penile mucosa, presenting as red, shiny, possibly eroded patch. It is associated with infection with oncogenic HPV types.

Sqamous cell carcinoma: Itch, irritation, pain, bleeding, discharge, ulceration or discovery of a tumor may herald sqamous cell carcinoma.

Kaposi's sarcoma was rare before the advent or AIDS. HIV-related Kaposi's sarcoma has a predilection for the mucosa, and penis and foreskin are common sites of patch, papulo, nodular and hemorrhagic forms. Phimosis can occur.

Angiokeratodermas are blue-purple, smooth papules on scrotum end penile shaft that appear and multiply during life.

Pearly penile papules are present as flesh-coloured, smooth, rounded papules, predominantly around the coronal margin of the glans, often arranged in parallel rows or concentric rings.

Molluscum contagiosum is usually sexually acquired infection and present as small, flesh-coloured, monomorphic, dome-shaped papules indented with a central 'umbilicus'.

Chronic idiopathic penile oedema is uncommon and thought to result from chronic/recurrent staphylo/ strepto cellulitis/lymphangitis of the prepuce, penis and sometimes lower abdominal wall.

Zoon's balanitis is a disorder of middle-aged and older uncircumcised men. Well demarcated, moist, shiny, bright red or brown patches involve glans and prepuce (often opposed in a 'kissing 'distribution).

Psoriasis: Anogenital skin is a common, and sometimes the only site of psoriasis. The Kohner phenomenon may contribute to this distribution. 'Inverse-pattern psoriasis' refers to the appearance of the disease on intertriginous skin in the natal cleft, gluteal folds and groins, between the dependent flaccid penis and preputial sac, and on the glans of uncircumcised men.

Lichen sclerosus: Lilac, slightly scaly, atrophic white patches or plaques with telangiectasia, purpura, bullae, erosions and ulcerations may be seen on penis. Other presentations are phimosis and paraphimosis.

Lichen planus manifests as itchy, red-purples, patches or plaques. Occasionally, a micropapular (lichen nitidus) or erosive form is seen.

Pyoderma gangrenosum is very rare. It may occur as a Kohner reaction to local trauma such as urological surgery, or may be associated with Behcet's disease, ulcerative colitis or CLL.

Bowen 's disease is a squamous cell carcinoma of the glans or prepuce presenting as a red, shiny, scaly patch. Extra agential disease may be associated with HIV infection, sunlight exposure and internal neoplasia.

Bowenoid papulosis is analogous to other manifestations of penile intra-epithelial neoplasia (PIN), e.g. Bowen's disease, and present as multiple warty lesions in younger sexually active males. The lesions are often pigmented in keratinized sites, and multiple and more inflamed in mucosal site.

Splinter hemorrhage. *Causes*:
Systemic diseases
Subacute infective endocarditis
Hypertension
Mitral stenosis
Diabetes mellitus
Rheumatoid arthritis
Internal malignancy
Systemic lupus erythematosus

Thrombocytopenia
Thyrotoxicosis
Trichinosis
Langerhans cell histiocytosis
Scurvy

Skin diseases
Psoriasis
Reiter's syndrome
Dermatitis/eczema
Exfoliative dermatitis
Onychomycosis
Mycosis fungoides
Pityriasis rubra pilaris
Pemphigus
Osler-Weber-Rendu disease

Drugs
Tetracyclines
Drug reactions (in general)

Miscellaneous
Hemodialysis
Peritoneal dialysis
Idiopathic

Calcinosis cutis presents as multiple, non-joinder subcutaneous swellings over various sites. It has been classified into four types - metastatic, dystrophic, iatrogenic and idiopathic. The nodules can become painful and disfiguring with ulcerative, infective and mechanical complications. Dermatomyositis, SLE and CREST classically manifest with dystrophic classification.

Diseases with dermal rash

1. SLE
2. Dermatomyositis
3. Psoriasis
4. Rheumatic fever
5. Reactive arthritis
6. Cryoglobulinemia
7. Still's disease
8. Sarcoidosis
9. Rubella
10. Dengue
11. Henoch-Schonlein purpura
12. Lyme disease
13. Iatrogenic

Uncommon genital conditions

Psoriasis on shaft of penis produces dull, red plaques covered with scale.

Lichen planus may affect the glans and prepu ce, but seldom the vulva. The lesions are flat, shiny, violaceous papules and are often itchy.

Lichen sclerosus et atrophicus may be seen on the prepuce, causing atrophy, depigmentation and contraction (which may lead to phimosis). Vulvar involvement may present with pruritus, and later produce contraction at the introitus.

A fixed drug eruption lesion is usually ovoid. The affected site is marked with post inflammatory hyperpigmentation.

Fever-Rash

Though a rash is usually generalized and pathognomonic of exanthemata, the term is often used to include all cutaneous eruptions.

Causes:

I. Acute illness of short duration
   1. Exanthemata: Measles, rubella, scarlet fever, enteric fever, generalized vaccinia, Kaposi's varicelliform eruption.
   2. Pyogenic: Erysipelas
   3. Allergic rashes: Acute allergy, drug rash, serum sickness, Henoch-Schonlein purpura
   4. Herpes zoster
   5. Rheumatic fever
   6. Infectious mononucleosis
   7. Dermatomyositis

II. Subacute or chronic illnesses of long duration
   1. SLE
   2. TB of skin – Miliary TB, papulonecrotic
   3. Erythema nodosum
   4. Lepra reaction
   5. Secondary syphilis
   6. PAN
   7. Panniculitis: Common from is characterized by nodules and plaques of dusky colour with relapsing fever and constitutional symptoms.

Sweets' syndrome: Acute febrile, neutrophilic dermatosis is characterised by sudden onset of fever, leucocytosis and cutaneous eruption. Tender, erythematous and well demarcated papules, plaques.

Cutaneous anthrax should be considered in differential diagnosis is cases presenting with ulcers vesicles or eschars with a recent history of exposure to naimal or animal products.

Cutaneous manifestations due to occult tumor

- Acanthosis nigricans (mainly ca of stomach)
- Thrombophlebitis migrans (pancreatic carcinoma)

- Dematomyositis (Tumors of female reproductive organs)
- Ichthyosis (lymphoma mainly)
- Pachyder moperiostosis (cancer lung)
- Pemphigus neoplastic type (myeloproliferative disorders)
- Bullous pemphigoid (malignancy of stomach, breast, lungs)
- Hypertrichosis lanuginosa (lung and colon cancer)
- Tripe palms - Accentuated palmar creases (lung cancer)

Differential diagnosis of psoriasis

Types of psoriasis	
Psoriasis vulgaris	• Discoid eczema - well defined, itchy circular lesions with crusting rather than scaling; the lesions show a predilection for the legs • Seborrhoeic eczema - ill-defined, browner lesions with greasy scale affecting the scalp, face, upper chest and flexures • Tinea corporis-well-defined, slightly itchy circular lesions with red, scaly margins and central clearing, with an asymmentrical distribution • Lichen simplex - ill-defined, itchy lesions with marked skin thickening, purplish colour and increased skin markings (lichenification)
Guttate psoriasis	• Pityriasis rosea - starts with a large herald patch, over several weeks, develops numerous small pink papules with a fine peripheral scale over the trunk and upper limbs; the papules fade within 6 weeks • Lichen planus - purple papules covered with white lines (Wickham's striae) with possible mouth and nail involvement
Napkin psoriasis	• Irritant dermatitis - weeping, erythematous lesions confined to the nappy area, but sparing body folds • Seborrhoeic dermatitis - erythema and scaling of the nappy area, often with lesions of scalp, face and axillae • Candidiasis - macerated, erythematous lesions with pustulation and satellite lesions
Nail psoriasis	• Onycholysis can occur in fungal nail infections, thyrotoxicosis, hypothyroidism, Raynaud's phenomenon and trauma • Nail pitting occurs in alopecia areata and occasionally in lichen planus
Erythrodermic psoriasis	• Drug reactions, eczema and cutaneous T cell lymphoma can all lead to erythroderma; these conditions are distinguished from psoriasis by the clinical history and skin biopsy changes
Palmoplantar pustulosis	• Hand eczema-ill-defined, itchy areas with vesicles rather than pustules • Fungal infection-unilateral or asymmetrical erythema with scaling, involvement of the toe clefts, nails and palmar eases

Infectious diseases and Infections

Meningitis: CSF protein > 200 mg means TBM unless proved otherwise. Acute polymorph reaction can occur in initial phase of TBM.

Measles: House-hold contacts (over 9-12 months) of measles patients should be vaccinated against measles within 3 days of exposure.

Anemia in malaria: *Possible factors -*

1. Hemolysis of infected RBCs
2. Hemolysis of uninfected RBCs
3. Dyserythropoiesis
4. Splenomegaly causing RBC sequestrations an hemodilution
5. Depletion of folate stores

Liptospirosis

1. Hemorrhagic fever with renal syndrome
2. Weil's syndrome. Severe leptospiremiawith jaundice, azotemia, hemorrhage, anemia and disturbed consciousness. Hepatic or renal manifestations predominate.
3. Atypical pneumonia syndrome resembling bilateral bronchopneumonia or ARDS. Leptospirosis should suspected in cases of rapidly developing pneumonia with severe myalgia.
4. Aseptic meningoencephalitis.
5. Myocarditis.

Lepto dipstick stick test is highly sensitive and specific test for diagnosis

Clinical syndromes of neurocysticercosis

Cerebral cysticercosis

- Seizure disorder
- Syndrome of increased intracranial tension
- Syndrome of intracranial space occupying lesion
- Syndrome of meningoencephalitis
- Psychiatric syndrome
- Stroke syndrome.

Ocular cysticercosis

Spinal cysticercosis

- Syndrome of compressive myelopathy
- Syndrome of radiculopathy.

Muscular cysticercosis

- Pseudohypertrophy of muscles.

Dengue vaccine: Dengue is not one virus but for 4 different viruses, or serotypes, each of which must be neutralized by the vaccine. Efforts to develop a therapeutic antibody for dengue are to focussed on a part of the virus called the envelop protein.

Chikungunya fever

Arthralgia refractory to other drugs - Use hydroxy chloro quine 200 mg od or Chloroquine phosphate 300 mg day for 4 weeks. Before using chloroquine, peripheral blood smear examination must be done to rule out malaria.

Since an immunologic etiology is suspected in chronic case, a short course of steroids may be useful.

Clinical features in Chikungunya fever

Common	Infrequent	Rare in adults but seen sometimes in children
Fever	Rash	Photophobia
Arthralgia	Stomatitis	Retro-orbital pain
Backache	Oral ulcers	Vomiting
Headache	Hyperpigmentation	Diarrhoea
	Exfoliative dermatitis	Meningeal syndrome Acute encephalopathy

Osteoarticular problems in chronic phase: Usually subside in one or tow weeks. In about 20% case they disappear after a gap of few weeks. In < 10% cases, they tend to persist for months. In<10% cases, the swelling disappears, the pain subsides but only to reappear with every other febrile illness for many months. Each time, the same joints get swollen with mild effusion and symptoms persist for a day or two after subsidence of the fever. Destroyed metatarsal head has been observed inpatients with persistent joint swelling.

Differential diagnosis

1. **Leptospirosis:** Severe myalgia localized to calf muscles with conjunctival congestion/or subconjunctival hemorrhage with or without oliguria or jaundice in a person with history of contact to contaminated water might suggest leptospirosis.
2. **Dengue fever:** Severe back pain with purpura or active bleeding might suggest dengue fever.
   Confirmatory laboratory diagnosis is possible.
3. **Malaria:** Periodicity for fever and alteration of consciousness/seizures should prompt a diagnosis for malaria.
4. **Meningitis:** High fever with neck stiffness or alteration of consciousness should prompt a through about meningitis. All cases of meningoencephalitis during an outbreak of CF must be suspected to have CF.
5. Rheumatic fever is more common in children and presents with fleeting (migratory) polyarthritis predominantly affecting the large joints. Modified Jones criteria should be the basis for diagnosis. Raised ASO titre and a history of recurrent sore throat are other points to be noted.

Management of osteoarticular problems

Rickettsial Diseases

Rickettsiae comprise a group of organisms that occupy a position between bacteria and viruses. A general characteristics of rickettsiae is that mammals and arthropods are natural hosts. Rickettsioses caused by organism within the genus of rickettsiae can be divided into the following subgroups.

1. *Typhus group:* Causing classical epidemic typhus caused by *Rickettsia prowazekii* and *Rickettsia typhi* transmitted by human body louse and rat flea respectively.
2. Spotted fever groups containing a large number of species Rickettsia rickettsii transmitted from rodents and other animals by ticks. Rocky mountain spotted fever is a prototype.
3. Scrub typhus caused by *Rickettsia tsutsugamushi* and transmitted by larval trombiculidae bites.
   New rickettsioses are tick borne lymphadenopathy (TBLA) and Dermacentor - borne - necrosis - eschar lymphadenopathy (DEBONEL).

HIV-AIDS

Fungal meningitis: Apart from C. neoformans, other fungi also cause meningitis. If facility for fungal culture is not available and if CSF smear shows evidence of fungal infection, then standard therapy with amphotericin can be started earlier to reduce mortality.

Resistance to Antiretroviral therapy

There is no ARV combination as yet to stop HIV replication. The effective ART most result in undetectable (< 50 copies/ml). The must common cause of therapeutic failure is a viral resistance as it indicates ongoing viral replication in presence of the inhibitory drugs. During ART the virological failure appears first. Immunological failure becomes evident much later, followed by clinical failure. Therefore, viral load monitoring is essential to detect virological failure so as to switch the therapy.

Recommendations for ART in pregnancy

1. **Pregnant females on ART:** Continue same ART. Efavirenz can be switched panarine or PI in first trimester.
2. Pregnant females with CD4 <250 cells/camm: Initiate ART as per adult ART guideline avoiding Efavirenz in first trimester (due to fetal teratogenic risks.

3. Pregnant females with CD4 > 250 cells/cumm, short course regimen for 28 weeks till delivery. Zidovudine + Lamivudine + Lopinavir/Ritonavir.

Radiology and Imaging

Differential diagnosis of bilateral upper lobe fibrosis

- Old healed tuberculosis
- Subacute silicosis
- Chronic sarcoidosis
- Coal worker's pneumoconiosis
- Ankylosing spondylitis
- Rheumatoid disorders
- Berylliosis
- End stage histiocytosis
- Late manifestation of radiation therapy for carcinoma breast
- Idiopathic upper lobe pulmonary fibrosis

Abnormal intraluminal gas

1. Large bowel obstruction and paralytic ileus.
2. Small bowel obstruction.

Comparison of large and small bowel obstruction features

Feature	Obstruction	
	Small bowel	Large bowel
• Bowel diameter	<3 and > 5	> 5
• Position of loops	Central	Peripheral
• Number of loops	Many	Few
• Fluid levels	Many, short	Few, long
• Bowel markings	Valvulae (all the way across)	Haustra (Partially across)
• Large bowel gas	No	Yes

3. Volvulus: (a) Sigmoid volvulus: An extremely dilated loop of sigmoid bowel forms two large compartments which look like a coffe bean (coffee bean sign). (b) Caecal volvulus - Caecum is displaced to upper left abdominal quadrant. This leaves the right lower quadrant area empty ('empty caecum' sign). Distal to the volvulus the large bowel is empty.
4. Toxic megacolon: Grossly dilated large bowel, typically the transverse colon, with 'thumb printing' evident.
5. Acute pancreatitis: A small sentinel loop (a collection of intraluminal gas) of bowel may be seen; the inflamed pancreas paralysing the adjacent bowel, making it adynamic.
6. Duodenal obstruction (congenital or acquired), gives the appearance of two gas bubbles, one in the duodenum and the normal gastric air ('double bubble' sign).
7. Meteorism: Although there are prominent bowel loops, there is no cut off point; the bowel has been likened to crazy paving.

Calcification on abdominal X-rays

Normal structures that calcify

- Costal catilage
- Mesenteric lymph nodes
- Pelvic vein clots (phlebolith)
- Prostate gland.

Pathological calcification

- Pancreatic: Chronic pancreatitis, parenchymal tissue
- Renal: Hyperparathyroidism. Renal tubular acidosis
  Renal calculi
  Medullary sponge kidney
- Vascular: Atherosclerosis, abdominal aortic aneurysm
- Gallbladder
  Biliary calculi,
  gallbladder fibroids
  (Leliomyoma)
- Appendix: Appendicolith
- Bladder: Calculi
- Teratoma
- Uterus: Fibroids.

Biliary gas seen as branching 'tree-like' streaks of black projected in the liver shadow.

Causes: (a) After ERCP with sphincterotomy, gas may travel from the duodenum into biliary tree as the sphincter of Oddi in the second part of duodenum is incompetent. Similarly after a gallstone has been passed, the sphincter may become dilated. Fistulation between gallbladder and adjacent bowel allows a route for gas into the biliary system. (b) Cholangitis — If the biliary ducts are infected with gas forming organisms, it will befound in the duct, creating a negative contrast to the surrounding soft tissue of the liver.

Mount Fuji sign: In hyperostosis frontalis interna. The sign is an imaging observation in case of tension pneumocephalus and occurs due tosurgery or trauma and the air gets trapped in bilateral frontal dural spaces, with a ball valve mechanism. In anterior cranial fossa the dura is thin and closely applied to bone, and the arachnoid is adherent to frontal bones; hence the air being trapped in subdural space of anterior cranial fossa. As the accumulation occurs more, it compresses the frontal lobes on both sides, making the CT of the brain resembling the silhouette of a volcano such as Mount Fuji.

Pneumatoceles are thin-walled, air-filled cysts that develop within the lung parenchyma. They can be simple emphysematous lesions, more often multiple thin-walled, air-filled cyst like cavities. Staph. pneumonia with pneumatocele is common in children, uncommon in adults.

Tree-In-Bud sign is a CT scan finding of chest with visibility of small airways. Dilatation of bronchioles due to luminal impaction with mucus or pus, and thickening of their walls due to peribronchiolar inflammation lead to visibility of bronchioles on thin section CT scan. Histopathologically, terminal tufts of tree-in-bud opacities represent inflammation with caseous material in respiratory bronchioles, whereas the stalks represent caseous material in terminal bronchioles. Tree-in-bud opacities are focal or multifocal, unilateral or bilateral. It is commonly associated with bronchopneumonia, invasive aspergillosis, viral bronchiolitis, endobronchial tuberculosis, pneumocystis pneumonia, bronchoalveolar cell carcinoma. Rare causes include RA, Sjogren's syndrome, :amgerjams cell histiocytosis, sarcoidosis, inhalation of toxic fumes or gases. Congenital causes include cystic fibrosis, dyskinetic cilia syndrome, yellow nail syndrome, or congenital immunodeficiency disorders.

Temporal arteritis: Evidence of a dark shadow halo on ultrasonography, arterial. wall oedema is considered to be a specific sign of active disease.

Hot cross bun sign on MRI is due to loss of pontine neurons and myelinated transverse, pontocerebellar fibres with relative preservation of corticospinal tracts which run craniocaudally. The sign can occur in multisystem atrophy-cerebellar (MSAC).

Miscellaneous

Poland's syndrome: or anomaly consists of unilateral absence or hypolplasia of pectoral muscle, most commonly involving the sternocostal portion of pectoralis major and a variable degree of hand digit anomalies including symbractyly.

Musculoskeletal problems associated with malignancy:

- Arthropathies
- Muscular disorders including polymyositis/dermatomyositis
- Scleroderma, panniculitis and fascitis
- Vasculitides
- Miscellaneous rheumatic syndrome

Bechet syndrome must be suspected in all cases who present with orogenital mucosal ulceration, scleritis/uveitis and also considered in DD of PUO.

Immunodeficiency and low mannose-binding levels Common variable immunodeficiency syndrome (CVID) characterized by failure of B-cell differentiation and defective IgG production leading to recurrent bacterial infection particularly of respiratory tract. ML deficiency increases infection susceptibility to a disease (e.g. meningococcal disease) or alters the natural history of disease, e.g. cystic fibrosis. CVID and chronic granulomatous disease.

Low serum ceruloplasmin level

- New born and infants
- Severe malnutrition
- Nephrotic syndrome
- Protein-losing enteropathy
- Congential ceruloplasminemia
- Severe hepatic insufficiency
- Acute hepatic infections

Kikuji-Fugimoto's disease is a rare self-limiting disorder characterized by fever and cervical lymphadenopathy. Diagnosis established by excision lymphnode biopsy and histopathology which shows histiocytic necrotizing lymphadenitis.

Maliedosis caused by B pseudomalle, has been referred to as the 'remarkable imitator' because of varied clinical presentations. Infections may range from subclinical towards a fulminant disease. Infections may be acute or chronic, localized or disseminated. Humans acquire the infection by inhalation of contaminated dust or when soil contaminated with bacteria comes in contact with abraded skin. The primary focus of infection may be the lung, skin and subcutaneous tissue.

PICA: Doctors must inquire about PICA whilst taking dietary history in case of unexplained hypokalemia and nutrient deficiency.

Hyperhomocystinaemia. Causes:

Primary

Inherited enzyme deficiencies

Cystathionine beta-synthase deficiency

C_{677} T mutation of methylene tetrahydrofolate reductase

Methionine synthase deficiency

Methylene tetrahydrofolate hornocysteine methyl transferase deficiency

Secondary

Physiological

Age

Male gender

Menopause

Lifestyle factors

Tobacco use

Coffee consumption

Vitamin deficiency

Folic acid deficiency

Cobalamin (vitamin B12) deficiency

Pyridoxine (vitamin B6) deficiency

Systemic disorders

Hepatic impairment
Kidney impairment
Diabetes mellitus
Systemic lupus erythematosus
Psoriasis
Anorexia nervosa
Hypothyroidism
Malignancies: breast, ovary, pancreas, acute lymphoblastic leukemia
Solid organ transplantation

Drugs

Methotrexate, phenytoin, anticonvulsants, azathioprine, theophylline, metformin, thiazide diuretics, colestipol, nicotinic acid, oral contraceptives.

Epicardial adipose tissue: Indicator of metabolic syndrome. Epicardial fat tissue tends to be higher in subjects with metabolic syndrome than in normal subjects and correlate s well with raised triglycerides. Hence echocardiographic assessment of epicardial adipose tissue can be used as an easy method of screening patients with cardiovascular risk.

Osteopoikilosis: An uncommon familial condition of unknown etiology characterized by uniform punctate, round or oval or linear streaks of bone in the epiphysis and metaphysis of long bones and pelvic bones. The condition can be distinguished from skeletal metastasis by the characteristic distribution, normal alkaline and acid phosphatase and by bone scan.

Non-vertiginous dizziness: *Causes.*

1. Pre-syncope (light headache due to transient cerebral hypoperfusion and not typical cerebral ischemia).
2. Migraine
3. Psychological dizziness, stress.
4. Multisensory dizziness.

Acute febrile encephalitis. Common causes are viral meningoencephalitis, tubercular and bacterial meningitis, sepsis associated encephalopathy and cerebral malaria. Meningitis is an important cause of febrile encephalopathy, especially in patients with HIV-AIDS.

Paraneoplastic plantar fasciitis and polyarthritis. Syndrome has been reported mainly with ovarian cancer and is thought to be a tumor associated autoimmune disease. It is characterized polyarthritis and flexion contractures of hands with palmar nodules due to palmar fasciitis. It has been reported to be due to metastatic gastric adenocarcinoma.

Pulmonary rheumatoid nodules in RA: They may be asymptomatic, regress with or without treatment, enlarge or persist. They may lead to complications like empyema, pleural effusion and pneumothorax and bronchopleural fistula.

Vulvar tuberculosis: An unusual presentation of disseminated tuberculosis.

Autoimmune polyglandular syn. type I is a rare disorder characterized by mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency.

INH induced lichenoid eruptions: INH may be the causative agent in different CDAR, and must be considered while confronting drug-induced cutaneous eruptions.

Summary of approved current gene therapy protocol

Disorder	Objective	Target cell	Mode of delivery
• ADA deficiency	ADA replacement	Blood	Retrovirus
• Alpha-1 antitrypsin deficiency	Replacement	Resp. epithelium	Liposome
• AIDS	Antigen presentation HIV inactivation	Blood, marrow Blood	Retrovirus
• Cancer	Immune function enhancement Tumor ablation	Blood, marrow, tumor Tumor	Retrovirus, liposome electroporation Retrovirus, non-complexed DNA
• Cystic fibrosis	Cystic fibrosis regulatory; trans membrane regulatory	Respiratory epithelium	Adenovirus , liposome
Familial hypercholesterolemia	Replacement of low density lipoprotein receptor	Liver	Retrovirus
Fanconi anemia	Complement group C gene delivery	Blood, marrow	Retrovirus
Gaucher's disease	Glucocerebrosidase deficiency replacement	Blood, marrow	Retrovirus
Hemophilia B	Factor IX replacement	Skin, fibroblasts	Retrovirus
Rheumatoid arthritis	Cytokine delivery	Synovium	Retrovirus

Occupational infection

Veterinary surgeons – Leptospirosis, Q fever.
Farm workers – Ringworm, leptospirosis, tetanus, BSE.
Poultry workers – Ornithosis, histoplasmosis, Newcastle disease.
Health workers – Hepatitis, HIV
Construction workers – Tetanus

Signs and Symptoms of Anaphylaxis

Organ or organ system	Characteristic signs and symptoms
Skin	Pruritus, flushing, urticaria, angioedema
Eyes	Ocular pruritus, excessive lacrimation, conjunctival injection
Respiratory system	Nasal congestion, rhinorrhoea, cough, hoarseness, stridor , wheezing, laryngeal oedema
CVS	Weakness, palpitation, tachycardia, hypotension, arrhythmias, shock, cardiac arrest
GI system	Cramping, nausea, diarrhoea, vomiting, abdominal distension, metallic taste

Elevated serum CA-125 levels

- Ovarian / peritoneal Ca
- Endometriosis
- Pelvic inflammatory disease
- Chronic kidney failure
- Cirrhosis

Fat embolism syndrome (FES) is a serious manifestation of fat embolism phenomenon characterized clinically by triad of dyspnoea, petechiae and mental confusion.

Consitions associated with fat embolism

- ***Trauma-related***
  - Long bone fractures
  - Pelvic fractures
  - Fractures of other marrow-containing bones
  - Orthopaedic procedures
  - Soft tissue injuries (e.g. chest compression with or without rib fractures)
  - Bums
  - Liposuction
  - Bone marrow harvesting and transplant
- ***Non-trauma related***
  - Pancreatitis
  - Diabetes mellitus
  - Osteomyelitis and panniculitis
  - Bone tumor lysis
  - Steroid therapy
  - Sickle cell haemoglobinopathies
  - Alcoholic (fatty) liver disease
  - Lipid infusion
  - Cyclosporin A solvent

Multiple connective tissue disease (MCTD)

1. Common symptoms:
   - Raynaud's phenomenon
   - Swollen fingers or hands
2. Anti U1 RNP antibody
3. Mixed findings
   A. SLE-like
      - Polyarthritis
      - Lymphadenopathy
      - Facial erythema
      - Pericarditis or pleuritis
      - Leucopenia or thrombocytopenia
   B. Scleroderma-like
      - Sclerodactyly
      - Pulmonary fibrosis
      - Esophageal dysmotility
   C. Polymyositis-like
      - Muscle weakness
      - Increased serum levels of CPK
      - Myogenic pattern of EMG

Requirements for diagnosis

1. Positive in either of two common symptoms
2. Positive anti-U1 RNP antibodies
3. Positive in one or more findings in two or three disease categories of A, B, C

Joint migration represents loss of normal congruity of the joint. It may result from severe damage to periarticular structures (e.g. ligaments and tendons in RA) or from severe joint damage in septic arthritis, osteomyelitis or a Charcot joint. Collapse of the acetabulum results in migration of the femoral head centrally in RA and superolaterally in osteoarthritis.

Vertigo with hearing loss. Causes:

- Acoustic neuroma
- Cholesteatoma
- Herpes zoster oticus (Ramsay Hunt syn.)
- Meniere's disease
- Otosclerosis
- Perilymphatic fistula
- TIAs or stroke involving anterior inferior cerebellar artery or internal auditory artery

Inflammatory ankle arthritis

Patients with isolated inflammatory ankle arthritis could be classified into (i) Lofgren's syndrome: Acute form of

arthritis which is the most common manifestation of sarcoidosis, often being the presenting symptom. (ii) Poncet's disease: Positive Mantoux test and mediastinal lymphadenopathy with or without unilateral hilar lymph nodes with central necrosis.

Symptoms and signs of inflammatory response

Clinical features

Fever or hypothermia
Tachypnoea
Altered mental state
Unexplained hyperglycemia
Inflammatory variables
Leukocytosis or leucopenia
Increased CRP
Increased procalcitonin
Tissue perfusion variables
Unexplained hyperlactatemia
Decreased capillary refill or
Skin mottling.
Oran dysfunction variables
Unexplained hypoxemia
Acute oliguria
Coagulation abnormalities
Ileus
Hyperbilirubinemia
Thrombocytopenia

Pathologic events in different organs

Organ/System	Presentation
Lungs	ARDS
Kidneys	Acute tubular necrosis
Brain	Encephalopathy
Coagulation system	DIC
CVS	High cardiac output, decreased ventricular ejection fraction, dilated ventricle, vasodilation, microcirculatory abnormality
Liver	Liver cell failure, canalicular dysfunction

Gardner's syndrome — is an autosomal disorder with features of colonic polyposis, dermal tumors, fibromas and neurofibromas. Congenital hypertrophy of retinal pigment epithelium manifests as black spots in the ocular fundus. Other manifestations include epistaxis, GI hemorrhage, cirrhosis due to liver telangiectasia, and high output cardiac failure from A-V malformations.

Dress Syndrome (Drug rash or reaction with eosinophilia) is drug hypersensitivity syndrome which begins around 2-6 weeks after exposure to a drug. It is a rare but severe type of reaction, most commonly with aromatic anticonvulsants, some antibiotics, antiviral and immunotherapeutic agents. It usually presents with fever, maculopapular rash, generalized lymphadenopathy, hypereosinophilia and hypogammaglobulinemia.

Influenza vaccine is an inactivated vaccine containing 3 strains of influenza of which the influenza A (H1N1) vaccine virus is derived from 2009 pandemic influenza A virus.

Mixed acid-base disorders: Common clinical settings:

1. Metabolic acidosis/resp. acidosis — Severe pulmonary, cardiopulmonary arrest.
2. Metabolic acidosis/Resp. alkalosis — Kidney failure with vomiting, severe liver disease.
3. Metabolic acidosis/Metabolic alkalosis — Kidney failure with vomiting, alcoholic ketoacidosis with vomiting.
4. Metabolic alkalosis/Resp. acidosis — COPD with vomiting or diuretic use.

Micronized Folvite 15-30 mg tab. o.d. for Euvolemic and Hypervolemic hyponatremia.

Urinary anion gap is used to differentiate between renal and extrarenal cause of non anion gap (NAG). The urinary NAG is defined as (UNa+ Uk-Ucl) and is indirect estimate of urinary ammonium excretion. Normal range is 10 to +10. In extra-renal causes of NAG acidosis, the kidney produces a large amount of ammonium chloride and urinary anion gap is largely negative (> –10), in renal causes of NAH metabolic acidosis the kidney is not able to generate ammonium and unable to excrete acid, hence the anion gap is largely positive (> +10).

Osmolar gap: Plasma osmolality can be calculated by the formula 2 × sodium (mg/l), + glucose (mg/dl) divided by 18 + urea (mg/dl) divided by 2.8. If the calculated osmolality differs from the measured osmolality by 15/msom/kgH_2O, it is called as osmolar gap.

Causes of osmolar gap: Ethanol, isopropyl alcohol, methanol, glycine, mannitol, ethylene glycol, glycerol, chronic kidney failure.

H. pylori is an important factor for high blood ammonia concentration in hepatic encephalopathy in chronic liver disease.

Roth spots have been traditionally linked with infective endocarditis, but have also been seen in leukemia and anaemia.

Circulation of RBCs through the normal spleen removes DNA from younger cells (Howell-Jolly bodies), sclerotic granules (Pappenheimer bodies) and target cells, their appearance therefore is marker of splenic atrophy (e.g.

in coeliac disease or sickle cell disease) or removal. Traumatic splenic rupture leads to seeding of splenic tissues and cells, giving rise to splenunculus in the peritoneal cavity retaining some immunological protection.

Body iron stores are regulated by iron absorption, this is where the defect lies in haemochromatosis. In secondary iron overload excessive breakdown of RBCs releases amounts of iron in excess of that required to synthesize new Hb (about 20 mg daily) and that absorbed from the gut (1 mg daily), resulting in damaging iron deposition in other organs such as liver, endocrine organs, pancreas and heart.

Rubella: Clinical diagnosis of rubella could be missed because (a) Rubella is a mild erythematous infectious disease which follows typically a benign clinical course. (b) The infection may present atypically with minimum lymphadenopathy and an evanescent rash.

(c) Typical rubelliform rashes may also be induced by other viruses like Chikungunya, Parvovirus B19 and Ross river virus.

Diagnosis: Acute rubella infection is usually established by demonstration of seroconversion of paired sera or by demonstration of rubella specific IgM antibodies in a single specimen. IgM antibodies usually attain their maximum concentration within 10 to 14 days after onset of illness.

Symmetrical peripheral gangrene (SPG)

Causes:

- Infection like streptococcus pneumoniae
- Meningococcemia
- Falciparum malaria
- Viral gastroenteritis
- DIC
- Low cardiac output states
- SLE
- Vasopressors
- Reaction to drugs (sulfamethazine, penicillin)
- Ergotism
- Acquired haemolytic anaemia
- Decreased levels of vitamin C
- Antiphospholipid syndrome

Severe magnesium depletion

Adequate Mg concentrations are required for release of PTH from parathyroid gland and also as an activator for adenyl cyclase. Severe hypomagnesemia (< 0.4 mmol/L) may be seen in any severe and prolonged diarrhoeal illness, but Crohn's disease is the most common association. IV magnesium chloride 20 mmol over 24 hours for a few days, restores parathyroid responsiveness.

Prion disease has a long incubation period, which can last for years but ultimately is fatal within weeks to months of its onset.

Causes of rash and fever — tropical cosmopolitan infections

Organism/disease	Vector/Exposure risk	Associated features
Dengue	*Aedes* mosquito, urban and rural	Myalgia, haemorrhage, shock
Chikungunya	*Aedes* mosquito, urban and rural	Polyarthralgia
Rickettsia	Ticks	
African tick typhus Mediterranean spotted fever Rocky mountain spotted fever	*Amblyomma* ticks rural/wilderness *Rhipicephalus* dog ticks, urban, suburban Ticks, rural/wilderness	Escharcommon, headache Eschar common Eschar rare
Scrub typhus -	Larvae trombiculid mites	Eschar common
Orientia tsutsugamushi	(Chiggers), rural	
Typhoid fever -	Faecal — oral, poor sanitation	Prolonged fever, splenomegaly
Salmonella typhi/paratyphi		
Leptospirosis	Exposure to rat/rodent urine (freshwater)	Conjunctivitis, myalgia
Schistosomiasis	Freshwater snails	Eosinophilia
Yellow fever	Mosquito-borne urban/rural	Jaundice
Lassa fever	Mastomys rodent urine, rural	Pharyngitis, retrosternal pain, encephalitis, hemorrhage
Ebola/Marburg	Unknown, ? monkeys/bats, rural/wilderness	Abdominal pain, D + V, hemorrhage
South American haemorrhagic fever		
West Nile virus	*Culex, Aedes* mosquitoes, urban	Encephalitis

Organism/disease	Vector/Exposure risk	Associated features
Measles		Cough, conjunctivitis, Koplik's spots Coryza, pneumonitis,
Varicella — Zoster virus		Pharyngitis, lymphadenopathy,
Epstein — Barr virus		splenomegaly Pharyngitis,
Cytomegalovirus	Blood, body fluids	Pharyngitis, lymphadenopathy splenomegaly
Toxoplasmosis	Cats	Lymphadenopathy, myalgia, hepatosplenomegaly
HIV	Sexual, IVDU	Pharyngitis, lymphadenopathy, splenomegaly
Rubella	Human	Coryza, arthralgia
Staphylococcus aureus	Human, IVDU	Shock, murmur
Staphylococcus pyogenes	Human	Pharyngitis, cellulitis, shock
Neisseria meningitis	Human	Shock, meningitis
Neisseria gonorrhoeae	Sexual	Septic arthritis
Syphilis, Treponema pallidum	Sexual	Genital ulceration

Factors increasing statin-induced myopathy

1. Major illness
   - Trauma
   - Severe infection
   - Hypoxia
   - Hypothermia
   - Uncontrolled seizure
2. Chronic illness
   - Chronic kidney failure
   - Chronic liver disease
3. Endocrine and metabolic disorders
4. Viral infections
5. Hypothyroidism
6. Metabolic acidosis
7. Drugs
   Fibrates
   Azole antifungals
   Calcium channel blockers
   Cyclosporin
   Warfarin
   Antidepressants (fluoxetine)

Differential diagnosis of joint pain

Life-threatening conditions

- Malignancy (leukemia, lymphoma, bone tumor)
- Sepsis (septic arthritis, osteomyelitis)
- Non-accidental injury

Joint pain with no swelling

- Hypermobility syndrome
- Idiopathic pain syndromes (e.g. sympathetic dystrophy, fibromyalgia)

Coronary artery media thickness and coronary artery disease: Coronary artery intima-media thickness can be determined by high resolution B mode ultrasonography. This provide information about the severity of atherosclerosis. Reduction in degree of atherosclerosis with statin therapy as observed in the carotid artery correlates with coronary angiographic observations.

Management of Gestational Hypertension

Stage I HT (BP> 140 mmHg systolic or > 90 mmHg diastolic)	Methyldopa 250-500 mg tds Calcium channel blockers e.g. Amlodipine 5-10 mg od Nifedipine 5-10 mg qds Diuretics e.g. Furosemide 20-40 mg bd β blockers (labetalol, atenolol) can cause IUGR (labetalol is safer compared to atenolol) hence should be used with caution
Stage II HT (BP > 160 mm Hg systolic or > 100 mmHg diastolic)	Combination of 2 or more drugs from the above (one from each group) as required
Hypertensive crises (BP> 180 mmHg systolic or >110 mmHg diastolic)	Nifedipine 10 mg orally can be repeated every 20 min to max of 30 mg.
	OR
	Nitroglycerine 5 /min IV as a continuous drip with BP monitoring

	Hydralazine 5mg IV bolus which can be repeated every 20-30 mins to a max. of 25 mg
	OR
	Labetalol 20 mg IV bolus followed by 40 mg every 10 mins till a max of 220 mg
	OR
	Sodium nitroprusside 0.25 g/kg/ min to a max. of 5 g/kg min. (Used rarely due to fear fetal cyanide poisoning)

Sarcoidosis is the commonest inflammatory condition to affect the heart and present with abnormal, focal areas of enhancement in RV and LV with wall motion abnormalities on cardiac MRI.

Takotsubo cardiomyopathy also known as the transient LV apical ballooning syndrome is a recently described acute coronary syndrome.

Sildenafil in pulmonary hypertension: Sildenafil selectively inhibits cyclic guanosine monophosphate specific phosphodiesterase-5 which is found abundantly in the lung. By this action it enhances nitrous oxide mediated pulmonary arterial pressure. It is useful adjunct to thrombolytic therapy in pulmonary embolism.

Flash pulmonary oedema is a condition characterised by sudden and recurrent episodes of dyspnoea at rest resulting from acute pulmonary venous congestion in the presence of a normal or well preserved LV systolic function. This is usually associated with bilateral renal stenosis or stenosis of a single survival kidney.

Mitral valve prolapse.

Echocardiographic mitral valve prolapse has been defined as single or bileaflet prolapsed atleast 2 mm beyond the long-axis annular plane, with or without leaflet thickening. The classical auscultatory finding is a dynamic, mid-to-late systolic click, frequently associated with a high-pitched, late systolic murmur. Specific manoeuvres (Valsalva, squatting and leg raises) demonstrates that click moyes within systole as LV volume and loading conditions change. Reduction of end-diastolic LV volume (squatting), decreasing contractility, or increasing after load (hand grips) will shift the click later into systole.

Patients with MVP have a higher risk of developing infective endocarditis. Factors include male sex, age > 45 years, presence of a systolic murmur and leaflet thickening and redundancy.

Alcohol septal ablation for HCM. A vessel supplying blood to the vessel, muscle is assessed through a thin plastic tube. A small balloon is inserted through the tube and inflated to prevent backflow of alcohol. 1-1.5 ml bf alcohol is then injected which causes clotting of the blood and blocks the supply to the part. There is over 50% reduction in muscle thickness post-procedure.

Transplant of stem cells in foetuses. Stem cell transplantation which uses mother's bone marrow to inject in the developing foetus to cure blood diseases. The donor cells are accepted by the foetus growing immune system. Many genetic diseases can be diagnosed in first 12 weeks of pregnancy.

Crimean-Congo hemorrhagic fever (CCHF). A particular variety of ticks, Hyalomma which is known to act as both a reservoir and a vector for several diseases is known to be present in the environment. Primarily found in cattle, sheep, goats and hare as amplifying hosts for the virus, transmission to humans occurs through contact with infected animal blood or ticks. Human to human transmission occurs by contact with infectious blood or body fluids. Documented spread of CCHF has also occurred in hospitals due to improper sterilization of medical equipment, reuse of injection needles and contamination of medical supplies. Cutting meat infected with the virus can also lead to spread to humans.

Cl.Fs. : Sudden onset with high fever, headache, backache, arthralgia, abdominal pain, vomiting. Other features include lymphadenopathy, rash and hemorrhagic phenomena such as petechiae. As the disease progresses, severe bruising, nose bleed bleeding gums, bleeding from upper bowel, and at injection sites occur on about the fourth day and last for about 2 weeks.

Diagnosis: Detection of antibodies against the virus.

Tr.: Ribavirin oral or IV. Supportive therapy.

Post-Chikungunya Chronic Arthritis (PCCA)

Chronic inflammatory polyarthritis can occur after acute chikungunya infection in some patients. It is seronegative and AntiCCP positive in majority.

Tr. with sulfasalazine with or without methotrexate is effective.

Distinguishing Parkinson's disease from Parkinsonism form of Multiple System atrophy

Urinary incontinence or orthostatic symptoms within one year history of motor symptoms suggests a diagnosis of MSAP and their absence suggests PD.

Mycophenolate mofetil

The drug is useful in renal transplantation and lupus nephritis. It has advantage of relatively less side-effects

and no nephrotoxicity. In primary nephrotic syndrome, though not the first line drug, it can be considered in those who fail to respond to corticosteroids or immunomodulatory medication, or relapse.

Heel pad sign

Though not pathognomonic, a heel pad thickness > 23 mm on radiograph may indicate acromegaly.

Joint pain with swelling

- Juvenile idiopathic arthritis
- Trauma
- Infection
  Septic arthritis and osteomyelitis (viral, bacterial, mycobacterial)
  Reactive arthritis (post-enteric, sexually acquired)
  Infection related (rheumatic fever, vaccination related)
- Inflammatory bowel disease
- Psoriatic arthritis
- Connective tissue disease (systemic lupus erythematosus, scleroderma, dermatomyositis)
- Sarcoidosis
- Metabolic (e.g. osteomalacia, cystic fibrosis)
- Hematological (haemophilia, hemoglobinopathy)
- Crystal arthropathy
- Tumor (benign/malignant)
- Developmental/congenital (e.g. spondyloepiphyseal dysplasia)

Rheumatic disease with subcutaneous nodules

1. Rheumatoid arthritis
2. Rheumatic fever
3. Erythema nodosum
4. SLE
5. Gout
6. Drug-induced (methotrexate)
7. Multicentric reticulohistiocytosis

Stem cell therapy

1. Infusion of heart's own stem cells can repair the damage caused to the organ after an attack and lead to cardiac regeneration.
2. Stem cells can be obtained from an individuals own body fat taken from one part of the body by liposuction.
3. Stem cell therapy for spinal cord injuries. The replacement cell therapy is based on the replacement of cell, with a view to regenerate axons and myelination of the regenerated axons.
4. Milk and wisdom teeth can be source of stem cells.

Urine in aminoaciduria

Maple syrup disorder	Burnt sugar smell
PKU	Musty or mousy odour
Tyrosinemia	Cabbage-like odour
Alkaptonuria	Urine turns black on standing

What's New

- **New guidelines for brain death.** The possibility of brain death being irreversible can be eliminated by continuous observation of the patient for a minimum of 5 minutes to confirm absence of the circulation before being declared death.
- Tenofovir (anti-viral drug) taken once daily reduces HIV risk to nearly half in injectable narcotic drug users.
- **Breastfeeding** helps protect against Attention Deficit hyperactivity, commonly diagnosed behavioural condition in children.
- **TMS therapy** involves using magnetic field externally to stimulate new cells in the brain. An electromagnetic coil is placed on the scalp at a predetermined site. This device then delivers focussed magnetic pulse to the brain.

  Indications:
  - Major depression
  - Tr. resistant depression
  - Auditory hallucinations
  - Schizophrenia
  - Bipolar disorder
  - Obsessive compulsive disorder
  - Eating disorders such as anorexia and bulimia

Advantages:

(1) Quick onset of therapeutic effect usually 2 to 4 weeks. (2) Painless procedure. (3) No anaesthesia required. (4) Outpatient therapy. (5) Fewer or no side effects.

- **Sono-thrombolysis:** The used of ultrasound waves along with the fibrinolytic agent has been shown to improve the outcome of patients with stroke. Application of ultrasonic waves can be done through intravascular route or transcutaneous route. The exact mechanism of benefits of sono-thrombolysis is not known, however the nitric acid released by vibrating endothelial cells and opening of collateral channels have been suggested.
- **Stem cell therapy in AMI:** Intracoronary infusion of either circulating progenitor cell (CPC) or bone marrow derived progenitor cells in patients with AMI have shown a reduction in infarct size and an increased ejection fraction.
- **Dental caries:** No more root canals. Stem cell therapy can regenerate the dentin pulp complex and consequently totally regenerate the tooth structure and function.
- **From skin to stem cells:** Human stem cells can be reprogrammed to become embryonic stem cells without the use of fertilised embryos. Embryonic cells start to divide and eventually become stem cells which are capable of transforming into any other cell type to cure several diseases.
- **Stem cells harvested from urine:** Urine derived stem cells can be directed to become multiple cell types. These cells can also form bone, cartilage, fat and skeletal muscle, nerve and endothelial cells which line blood vessels. These stem cells represent virtually a limited supply of urology related conditions such as kidney disease, urinary incontinence and erectile dysfunction.
- **Down's syndrome:** Scientists have shown that a naturally acting X chromosome "off switch" can be rerouted to neutralise the extra chromosome responsible for trisomy 21 (Down's syn.).
- **Ultrasound via a skin patch** helps venous ulcers significantly and accelerate tissue repair. The ultrasound patch weighs 100 gm and is connected to two lithium batteries which are fully rechargeable.
- **Intramuscular ACTH stimulation test** for assessment of adrenal function. 25 units of ACTH is injected IM and blood samples taken after 60 minutes for estimation of cortisol. Patients with post-ACTH cortisol <18.0 mg/dl are diagnosed as having adrenal insufficiency.
- **Regenerative therapies:** Infusion with allogeneic mesenchymal stem cells have the potential to regenerate alveolar tissue by themselves or by secreting growth hormones. Specifically, vascular-endothelial growth factor (VEGF).
- **Oral diarrhoeal vaccine (ETEC):** A vaccine against E. coli, a primary cause of diarrhoea in children.
- One shot immunity against flu strains. A vaccine that could protect against most or all influenza strains without the need for annual vaccinations.
- **Wegener's granulomatosis:** Antineutrophil anticytoplasmic antibody (CANCA) is very specific for WG and is being used for diagnosis and monitoring the disease.
- **Intravenous Ulinastatin in severe pancreatitis** prevents new organ dysfunction and reduces mortality in subjects with severe pancreatitis.

  Dose: IV infusion of 200,000 IU over one hour every 2 hours for 5 days with standard supportive care.
- **Single glucose challenge test for diagnosis of Gestational DM:** In the antenatal clinic, a pregnant woman is given 75 gm of oral glucose without regard to the time of last meal. A various blood is collected after 2 hours for estimating plasma glucose. GDM is diagnosed if 2 hours plasma glucose is ≥ 140 mg/dl. The test is economical and the patient need not corne fasting.
- **Takotsubo cardiomyopathy:** LV apical ballooning is a novel acute coronary syndrome. It is characterized by regional systolic dysfunction involving apex and mid section of LV. This can be seen in left ventriculogram. It is not associated with any obstructive CAD.

New conjugate typhoid vaccine: (for children and adults) gives longer period of immunity.

Microneedle patch to replace TB skin test: A patch with tiny biodegradable needles that can penetrate the skin with the test there is little room for user error, because the depth of delivery is determined by the microneedle length rather than the needle insertion angle. The test is painless and easy to deliver.

Dental CBCT is a three dimensional imaging modality for dental use, dedicated specifically to maxillo facial imaging.

Routine applications

- Evaluation of the height, width and nature of bone available for implant placement.
- Providing virtual implant simulation and assessing their proximity of implant to vital structures.
- Localization of impacted teeth and assessing their proximity to vital structures.

Other applications

- Endodontic applications: Identification of accessory canals, anomalous/atypical canals, calcified canals, elucidation of root resorption, periapical pathosis, etc.
- Periodontal applications: Detection and characterization of the bony aspects of periodontal disease.
- Postoperative applications: Implant evaluation, assessment of endodontically restored teeth for overextended obturation material, broken instruments within the canal or perforations.
- Evaluation of dentoalveolar trauma: Root fractures, luxation, displacement of teeth, and alveolar fractures.
- Evaluation of jaw lesions: Localisation and characterisation of various jaw cysts, tumors, fibro-osseous conditions, etc.
- Imaging of the temporomandibular joint: Evaluation of osseous changes of the TMJ.
- Caries detection: For those incipient, mild, proximal caries which are not visualised on OPG and IOPA.

Tr. of HIV: A combination of Decitabine and Gemcitabine is an effective treatment for HIV virus. The drug combination has been shown by lethal meutogenesis could obliterate HIV by causing the virus to mutate to a point when it was no longer infectious.

H1N1 encephalopathy: Apart from exacerbation of underlying chronic disease, pulmonary and cardiac complications of H1N1 influenza, also cause seizures, encephalopathy and status epilepticus.

Malarial vaccine: Contains live malaria parasites collected through a process of dissecting the salivary glands of mosquitoes. These immature parasites (sporozoites) are then weakened so that they cannot cause illness and incorporated into a vaccine.

Carotid bodies and hypertension: Removing one of the carotid bodies located at the bifurcation of the carotids could dramatically reduce BP in patients who do not respond to medicines.

Vaccine against MERS (Middle East respiratory syndrome). (COV) has been developed against the illness, which can spread from person to person and has high mortality rate.

Tr. of DM: DDP-4 inhibitor that does not require dose adjustment in adults with DM2. Linagliptin 5 mg tab. OD is the only drug which is not associated with cardiovascular events.

Pacemaker implant for treatment resistant GERD.

Vaccine for Japanese B encephalitis now available.

Implanted catheters: Multiple drug resistant bacterial biofilms on implanted catheters including vascular and Foley catheters. This suggests that catheters should be removed as early as possible to prevent biofilm development in them.

Single test to detect cancer: Tumor prefilling (TP) test will help search for genetic alteration which is driving the growth of tumor-lung, breast, biliary tract, ovarian, thyroid and urinary tract cancer.

Tooth transplant for an injured blind eye. During the technique osteo-odonto-keratoprosthesis, one of patient's front tooth and a part of jaw were removed and used as a cradle holder for a false lens.

Chronic Hepatitis B infection

Telbivudine plus Tenofovir in combination exhibited significant biochemical responses over the period of one year however it was not higher than that seen with monotherapy.

Renal Sympathetic denervation for resistant hypertension

Uncontrolled hypertension (HTN) accounts for significant morbidity and mortality. Renal denervation therapy can improve the control of high BP.

Drug to cure Hepatitis C

The drug combination of Sofosbuvir and Ledipasvir stopped the virus replicating in 97% of patients. An increasing number of people infected with virus are developing cirrhosis and liver failure.

Nitrous oxide gas therapy (with help of a ventilator) to treat meconium aspiration syndrome in the new born. It dilates the pulmonary arteries and the pressure in the arteries goes down.

What's New

Dabigatran can be used as anticoagulant for stroke prevention in AF. Dose: 150 mg for patient with low risk of bleeding 110 mg if high risk of bleeding. Contraindicated in vascular heart disease and in those with prosthetic valves.

Echocardiography in pulmonary embolism

Acute PE may lead to RV pressure overload and disturbed RV ejection pattern (so called 60–60 sign), or on depressed contractility of the RV free wall compared with RV apex (McConnell)

Takotsubo cardiomyopathy Broken heart syndrome or stress induced cardiomyopathy is typically a transient heart dysfunction of the apical or midsegments of the LV that occurs in presence of acute emotional stress. It mimics acute MI with concomitant rise in biomarkers, ECG, 2 D Echocardiography abnormalities such as LV dysfunction with regional wall motion abnormality, no significant coronary artery disease on angiography. It is a variant of dilated cardiomyopathy.

Artificial pancreas endocrine: A device which monitors blood glucose in patients with diabetes and automatically adjusts levels of insulin entering the body. Currently available insulin pumps deliver insulin after taking readings from glucose meters, but these two components are separate. It is the joining together of both parts into a "closed loop" that makes an artificial pancreas.

Diabetes with Vitamin D Deficiency may be at higher risk of vascular complications including coronary artery disease.

Rhabdomyolysis is a syndrome characterized by muscle necrosis which causes the release of myoglobin into the blood stream. The manifestation range from asymptomatic elevation of muscle enzymes to lifethreatening cases with extremely high enzyme levels, electrolyte imbalance and acute kidney failure.

Symptoms include dark urine, muscle weakness and fatigue.

Laryngopharyngeal reflux disorder: An abnormal amount of reflux of the contents of the stomach passes all the way through the upper oesophageal sphincter into the back of the throat reaching the larynx and pharynx. Symptoms include hoarseness, frequent throat clearing, bitter taste in the mouth, referred ear pain and postnasal drip. Treatment for severe LPR is fundoplication which tightens lover oesophageal sphincter.

Endobranchial ultrasound: EBUS combines an endoscopic image with an ultrasound probe giving sonographic images through the airway wall. Indications, for EBUS (1) Staging of lung cancer, (b) Mediastinal lymphadenopathy, (c) Therapeutic uses (d) Assessment of airway wall infiltration and peripheral nodule. Anticoagulants should be stopped a week before the procedure. Benign granulomatous disorders like TB and sarcoidosis are most common cause of mediastinal lymphadenopathy. EBUS helps to reach these nodes as a minimally invasive procedure to take aspirations under real-time ultrasound guidance.

Hypocalcemic cardiomyopathy: Due to severe Vitamin D deficiency. The physiological basis is impaired intracellular calcium metabolism which plays an important role in the pathogenesis of CHF.

Haematology

Patients with pernicious anemia have a higher risk to develop GI malignancies such as gastric adenocarcinoma, carcinoid tumors and oesophageal squamous cell carcinoma.

Trans-sternal mediastinal biopsies—smaller masses and nodes may be difficult to approach directly. While it is often possible to use a transpulmonary route. The chances of pulmonary complications makes it more desirable to use extra-pulmonary approaches, one such is transsternal route and the simplest method is to lightly tap the needle into the manubrium sternum which is a thin bone and then enter the lesion posterior to the sternum and biopsy it.

New drug for leukaemia: Cells when they are born are destined to die and cancer of leukaemia cells, delays that death by using a protein called BCL2 that stops the normal time of death. The drug Venetoclax works by specially blocking the action of BCL2. The drug is given orally everyday as a pill. 20 mg/d increased to 400 mg over a five week period.

Drugs with multiple action.

Danazol

- Aplastic anemia
- Dyskeratosis congenital
- Endometriosis
- Gynecomastia
- Benign fibrocystic breast disease
- Menorrhagia
- Hereditary angioedema
- Idiopathic thrombocytopenic purpura

Renal

Measurement of renal function: It has been noted that serum creatinine is the least accurate, while the radionuclide GFR test is the most accurate.

Renal calculi: DECT allows to differentiate urate from monourate cystals. Uric acid can be managed medically, while non-uric acid calculi need ESWL or surgery.

Pollution trigger Alzheimer's, magnetic particles produced by car engines release free radicals in brain and disrupt cellular functions.

Lower blood flow, first sign of Alzheimer's: Using techniques such as MRI and PET show a decrease in the blood flow in the brain. The study also found that changes in cognition begin earlier in the progression.

Eating epilepsy: In the rare variety of seizures eating is a precipitating factor. The a affected area in such patient's brain is located in the left dominant lobe that controls comprehension and expressive speech. By a surgery called multiple subpial transection, brain tissues are not removed, only holes are made on the brain to stop the electrical impulses. The seizures may not completely disappear but the frequency is considerably reduced. The patient is advised to continue the drugs for one to two years.

Expanded dengue: The term has been carried by WHO to describe cases which do not fall into either dengue shock syndrome or dengue hemorrhagic fever. The typical manifestations noted in dengue can be multisystemic and multifetal. In clinical practice the occurrence of a typical should prompt the clinician to investigate for dengue.

Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart have been increasingly reported in DHF and also in dengue patients who do not have evidence of plasma leakage.

These unusual manifestations may be associated with co-infections or complications of prolonged shock and can be clubbed under the expanded dengue syndrome.

Fast acting drug against rabies.

The drug, rabies human monoclonal antibody (RMAB) Rabishield automatically precludes chances of transmitting blood-borne infection that are present in rabies immunoglobulin, the current line of treatment for severe dog bite cases. WHO defines category III animal bites as single or multiple transdermal animal bites a scratches contamination of mucous membrane with saliva from licks or broken skin and exposure to bats.

Aquaholism: Causes by water glut can be deadly. It can bring about a condition like hyponatremia. It can also cause secondary hypokalemia.

Single pill a day treatment for HIV/AIDs patients life long. Doltegravis (DTC) + Abacavir + Lamivudine is the most promising regime.

CNS

Implantable capsule for Alzheiner's disease: One of the hypothesised causes of the disease is the over-accumulation of the protein amyloid beta (A beta) in different areas of the brain. This results in the deposition of aggregated protein plaques that are toxic to neurons. One of the most promising ways is to 'tag" the Abeta proteins with antibodies that signal the patients own immune system to attack and clear them.

The capsule contains cells that have been genetically engineered to produce antibodies against Abeta. The implant can deliver a steady and safe flow of antibodies. It is implanted in the tissues under the skin.

Moyamoya disease: It is an idiopathic cerebrovascular occlusive disorder characterized by progressive stenosis of the distal internal carotid arteries and by collateral vessel formation. On conventional X-ray, angiography, these collateral vessels have the appearance of a puff of smoke described as moyamoya in Japanese. Treatment involves creating stents to improve the circulation and prevent brain ischemia.

Radiology

X-ray—The Golden S sign: In case of carcinoma of the lung when the peripheral lung collapses and the central portion is prevented from collapsing by the presence of a mass. The relevant fissures resemble an S. The Golden S sign can CT scans.

Although typically seen with right upper lobe collapse, the S sign can also be seen with collapse of the other lobes and has been demonstrated on lateral chest radiography.

Boomerang sign: MRI of the brain shows hyperintense signal in the splenium of corpus callosum.

Dual energy CT: It is a technique where patient is scanned at two or more different energies. There are a number of applications for this technique e.g., Gout.

The DECT shows crystal deposition in the joint. It is also possible to quantify the overall tophus burden and can be used for follow up to document response to treatment. Differential diagnosis of pulmonary infiltrates in HIV infection.

1. TB
2. A typical mycobacterosis
3. Opportunistic infections
   - Pneumocystis is carin
   - Cytomegalovirus
   - FB virus
   - Toxoplasmosis
   - Fungi
3. Kaposis sarcoma
4. Non-infectious lymphocytic interstitial pneumonitis
5. Lymphocytic granulomatosis

Index

Page numbers followed by *f* refer to figure and *t* refer to table

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z