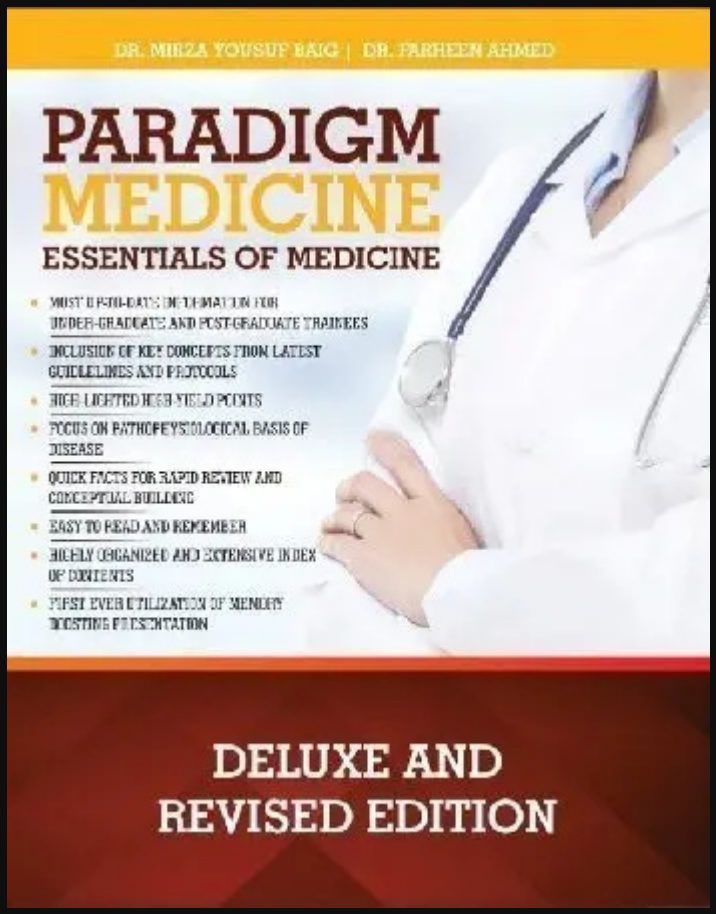
DR. MIRZA YOUSUF BAIG | DR. FARHEEN AHMED
PARADIGM
MEDICINE
ESSENTIALS OF MEDICINE
DELUXE AND
REVISED EDITION

PARADIGM

MEDICINE

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Dr.MirzaYousufBaig

MBBS (DUHS), Ex Post-graduate Trainee FCPS (DZH)

Registrar CCU/ ICU, Dr. Ziauddin Hospital

External Faculty Medicine/ Physical Therapy/ Medical Technology (Ziauddin University)

Dr.FarheenAhmed

MBBS (BAQAI), Ex Post-graduate Trainee FCPS (DZH)

PARADIGM MEDICINE

AUTHORS: DR. MIRZA YOUSUF BAIG, DR. FARHEEN AHMED

EDITOR: DR. MIRZA YOUSUF BAIG, DR. ABDUL RAHIM KHAN

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1. GENERAL MEDICINE

1.1. MEDICINE

"Medicine is the science of diagnosis, treatment and prevention of disease."

- The practice of medicine begins with medical interview which is followed by physical examination. Both are used to formulate a list of differential diagnoses. Different investigations are then used to include or exclude a diagnosis. In the meanwhile patients are managed symptomatically. Management may be started on the basis of suspicion if there is risk of worsening of condition or if the symptoms are debilitating or the suspicion is very high. Once a diagnosis is made, specific treatment is started or continued if already started.Necessary health education is imparted to the patients. The practice can occur in setting of clinics/basic health care units (general practice) or hospitals (hospital medicine). The above steps can vary depending on the need e.g. shorter history and earlier management is needed in case of patients presenting in emergency. In case of critical patients maintaining circulation, airway and breathing and delivery of advanced cardiac life support may even supersede history taking.

Medical care can also be divided into three categories:

1. Primary care services: provided by general practitioners, medical officers, nurses, health visitors at first contact of patient with medical care. These cover common acute or chronic illnesses, preventive care and health education.
2. Secondary care services: provided by specialists and their medical and para-medical staff where patients from primary care services are referred because of need of some expert treatment.
3. Tertiary care services: include advanced medical investigations and treatment, provided by specialists and their teams in hospitals.

1.2. ADMISSION ORDERS

Admission orders are written to ensure proper initial care to the admitted patient. These orders should include (Also see Table 1.1):

- Patient name and identification
- Admission location
- Name of attending care-taker doctors
- Reason for admission
- Working diagnosis:
- Condition of patient
- Whether needs monitoring or not
- Frequency of monitoring of vital signs and any special vitals to monitor
- Nursing instructions:
- Medications prescription
- Activity allowed to patient
- Whether there is need for isolation:
- What labs to send and is there any serial investigations needed
- Any special studies including ECG, x-rays, interventions
- Consults from other specialties
- IV fluid orders
- Diet orders
- Allergies
- Assess need for peptic ulcer prophylaxis
- Assess need for DVT prophylaxis
- Assess need for bone supplements
- Assess need for ACE inhibitor/ Aspirin

- Transfusion orders
- Any need for therapists like respiratory, speech, physical, etc.
- Advance directives

TABLE 1.1: ADMISSION ORDERS
"ADMIT VITALS AND PHYSICAL EXAM"
Reference: Harrison's manual of internal medicine

A = Admit	**P = Peptic ulcer prophylaxis**
D = Diagnosis	**H = Heparin**
M = MD	**Y = Yank**
I = Isolation requirements	**S = Skin care**
T = Telemetry	**I = Incentive spirometry**
V = Vital signs	**C = Calcium**
I = IV	**A = ACE inhibitor and aspirin**
T = Therapists	**L = Lipid panel**
A = Allergies	**E = ECG**
L = Labs	**X = X-rays**
S = Studies	**A = Advance directives**
A = Activity	**M = Medications**
N = Nursing orders	
D = Diet orders	

1.3. HISTORY TAKING

IDENTIFICATION:
- Name
- Age
- Gender
- Address
- Race
- Occupation
- Marital status
- Religion
- Source of history: patient or attendant
- Reliability of informer(s)
- Date and time of interview

COMORBIDS:
List the main comorbid diseases which the patient is suffering from.

PRESENTING COMPLAINTS:
It includes the main complain for which the patient is seeking medical attention. If there are multiple complains, they should be listed in chronological order.

HISTORY OF PRESENTING COMPLAINTS:
Describe the details and course of each presenting complaint in terms of following:
- Timing: onset, duration and frequency
- Quality/ character: In case of pain, ask about the site of maximum pain, any radiation or referral and whether pain is intermittent or continuous. In case of fever record pattern of fever.
- Quantity/ severity
- Setting in which the symptom occurred
- Progress
- Alleviating and aggravating factors
- Associated factors

SYSTEMIC REVIEW:

Ask patient about complains from different systems in order not to miss any pertinent positive or negative findings.

- **GENERAL:** usual weight, weight gain or loss, generalized weakness, fatigue, fever, appetite.
- **CARDIORESPIRATORY:** chest pain/ discomfort, dyspnea/ shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, palpitations, edema, cough, sputum, hemoptysis, wheezing,
- **PERIPHERAL VASCULAR:** intermittent claudication, leg cramps, varicose veins (swollen tortuous veins), calf/ leg/ feet swelling, change in color of fingers or toes or limbs.
- **GASTROINTESTINAL:** dysphagia, odynophagia, heartburn, appetite, nausea, vomiting, change in bowel habits, bleeding from rectum, black tarry stools (melena), constipation, diarrhea, abdominal pain/ colic, food intolerance, excessive belching or passing of gas, jaundice, anorexia.
- **NEUROLOGIC:** headache, dizziness, vertigo, fainting, blackouts, seizures, weakness, paralysis, numbness or loss of sensations, tingling or pin-prick/ needle sensations, allodynia, tremors, abnormal movements, involuntary movements, stiffness, attention deficit, speech disturbances, change in orientation, memory weakness or loss,
- **GENITOURINARY:** frequency, urgency, hesitancy, burning micturition or pain on micturition, hematuria, pus in urine, gravel in urine, loin pain, polyuria, nocturia, incontinence, dribbling, penile discharge, hernia (swelling), testicular pain, scrotal swelling, loss of libido, erectile dysfunction, premature ejaculation, impotency, infertility, irregular menses, dysmenorrhea, polymenorrhea, menorrhagia, oligomenorrhea, intermenstrual bleeding, premenstrual tension, vaginal discharge, vaginal itching, vaginal sores, vaginal lumps, something coming out of vagina, menopause, postmenopausal bleeding, abortions, dyspareunia.
- **MUSCULOSKELETAL:** muscle/ joint pain, stiffness, backache, neck pain, muscle trauma, swelling of joints, painful joints, limitation of movements/ activity, fracture.
- **HEMATOLOGIC:** pallor, easy bruising and bleeding, transfusion reactions
- **ENDOCRINE:** polyphagia, polydipsia, polyuria, weight gain/ loss, heat or cold intolerance, excessive sweating, change in glove or show size.
- **SKIN:** itching, rashes, lumps, dryness, color changes, sores, changes in nails or hair, change in size or color of mole.
- **HEAD, EYES, EAR, NOSE, THROAT:** headache, head injury, dizziness, light-headedness, change in vision, eye pain, red eye, tearing/ lacrimation, double vision, blurred vision, spots/ specks in vision, flashes, hardness of hearing, tinnitus, vertigo, ear-ache, discharge from ear, colds, nasal stuffiness, nasal discharge, nasal itching, nose-bleeds, facial pain, complains regarding teeth and gums, bleeding gums, sore tongue, dry mouth, sore-throat, hoarseness of voice/ change in voice.
- **NECK:** neck lumps, glandular swellings, goiter, neck-pain, neck-stiffness.
- **BREASTS:** breast lumps, breast pain/ discomfort, discharge from nipple.
- **PSYCHIATRIC:** hallucinations, delusions, illusions, nervousness, tension, mood disturbances, depression, memory change, behavioral change, suicide attempts.

PAST HISTORY:

Assess past history of patient in following areas:

- Medical
- Surgical
- Gynecologic/ obstetric
- Psychiatric
- In case of children ask about prenatal, natal and postnatal history, developmental milestones and vaccinations.

PERSONAL HISTORY:

- Nature of present job
- Education status.
- Dietary pattern
- Life-style
- Hobbies and daily activities

- Important life events.
- Exercise
- Allergies
- Vaccination status
- History of travel abroad
- Which jobs has he done in past
- Any chemical or radiation exposure
- Any contact history with pets/ animals
- Any screening tests taken
- Use of illicit drugs/ smoking/ alcoholism/ chewable tobacco
- Sexual history: sexual behavior, risky sexual practices.
- Sleep habits
- Appetite
- Bowel and bladder habits?

MENSTRUAL HISTORY:

- Age of menarche
- Interval between periods
- Duration of menses
- Regularity
- How much flow?
- Any history of dysmenorrhea
- Any vaginal disharge
- Last menstrual period
- One prior menstrual period
- Intermenstrual bleeding
- Post-coital bleeding
- Amenorrhea
- Age of menopause
- Perimenopausal symptoms
- Postmenopausal bleeding/ discharge

FAMILY HISTORY:

- Family history of similar disease or any other disease like asthma, coronary artery disease (specifically coronary artery disease), diabetes, hypertension, dyslipidemias, stroke, thyroid disease, renal disease, cancer, tuberculosis, seizure disorder, allergies, psychiatric illnesses, suicide, etc.
- Especially enquire about any deaths in family and cause of deaths
- Draw a family tree especially if any inherited disorder is suspected.

SOCIOECONOMIC HISTORY:

- Occupation and socioeconomic class
- Home situation
- Any care-taker or social support
- Nature of family relations
- Number of dependents on the patient
- Home surroundings

1.4. PHYSICAL EXAMINATION

Before starting any examination make sure of following:

- Introduce yourself to the patient
- Inform what you are going to do and ensure that it will cause any pain
- Build a rapport with kind words
- Take consent for examination
- Expose the area which you are going to examine. Respect the modesty of patient especially females.
- Wash and warm hands before beginning examination

1.4.1. GENERAL PHYSICAL EXAMINATION

GENERAL SURVEY:

Cast a quick and effective glance on the patient and note the following:

- Apparent age
- Gender
- Apparent height
- Apparent weight
- Posture/ position
- Consciousness
- Orientation to time, place and person
- Comfort level/ distress
- Any particular smell/ odor from the patient
- Hygiene and attire
- Any ins and outs (foley's catheter, iv cannula, chest tube drain, etc.

VITALS:

- Pulse (also check whether pulse is regular, irregular, bounding, feeble or thready)
- Blood pressure (check whether patient is on inotropic or vasopressor support)
- Respiratory rate (comment on rate and character of respiration like gasping, sighing, labored, etc.)
- Temperature
- Oxygen saturation
- Pain (site and grade of pain)

SEQUENCE OF GENERAL EXAMINATION:

- Includes a head-to-toe general assessment:
- Ask the patient to lie down. Check temperature.
- Examine hands and nails for anemia, jaundice, clubbing, leuconychia, koilynychia, splinter hemorrhages, pitting, sweating, dryness.
- Note any tremors in hands or any abnormal posturing like carpopedal spasm, waiter's-tip hand, claw hand, etc.
- Check fingers for presence of joint deformities like Bouchard's or Heberden's nodes, swan-neck deformity, button-hole deformity, mallet finger, etc.
- Examine fingers for cyanosis.
- Check palms for presence of Duputren's contracture, palmar erythema or Janeway lesions.
- Check pulse and note: rate, regularity, character, volume
- Palpate for epitrochlear lymph nodes.
- Take blood pressure. Count respiratory rate in 30 seconds to one minute.
- Check scalp and hair for alopecia or brittleness of hair.
- Note the condition of skin whether features are coarse as in hypothyroidism.
- Notice the facies as some diseases are associated with particular facies e.g. moon face of Cushing's disease, hypothyroid face. Note any rash on face e.g. butterfly rash of SLE.
- Check parotid glands for swelling or pain.

- Examine eyes for jaundice, anemia, redness or any other abnormality.
- Check nose-tip, ear-lobes, tip of the tongue and lips for cyanosis.
- Check tongue for dryness, cyanosis or pallor.
- Note the dental hygiene status.
- Check the throat with a tongue depressor.
- Examine chest for gynecomastia, spider naevi or prominent veins. Note if there is hirsutism (excessive hair growth) or loss of hair.
- Examine abdomen for caput medusa, striae, etc.
- Palpate for enlargement of inguinal lymph nodes.
- Note sacral and ankle edema and grade edema.

Now position patient at 45 degrees angle and examine for jugular venous distension.

- Then ask patient to sit up and examine from front for thyroid gland. Also check axillary lymph nodes.
- Go behind the patient's back and complete the examination of thyroid. Also examine cervical lymph nodes (including sub-mental, sub-mandibular and supra-clavicular) and posterior group of axillary lymph nodes.
- Never forget to cover the patient once examination is complete.
- Thank the patient and examiner at the end.

1.4.2. RESPIRATORY EXAMINATION

EXAMINATION OF FRONT AND SIDES OF CHEST:

- Ask the patient to lie down and expose the chest for examination:
- Stand at the foot-end of the patient and do a thorough inspection.
- **Inspection:**
- Count the respiratory rate ideally over one minute.
- Notice the type of respiration: abdominothoracic, thoracoabdominal.
- Observe the character of respiration: sighing, labored, gasping, Cheynes-Stokes, etc.
- Check the shape of the chest: normal elliptical, asthenic (thin lean), sthenic (fat), barrel-shaped, pigeon-chest (pectus carinatum), funnel chest (pectus excavatum), etc.
- Note any deformities like Harrison's sulcus, rickety rosary, etc. Notice any bulge or flattening of chest.
- Notice any prominent veins, scars or pulsations.
- Compare movements of both sides of chest

PALPATION:

- Move hands gently across the whole chest to palpate for tender areas or crepitus.
- Palpate the position of the trachea notice any deviation. A slight deviation to the right can be normal.
- Palpate and localize the apex beat (usually in the fifth intercostal space just medial to the mid-clavicular line).
- Check for chest movements by placing hands firmly on the chest at different levels.
- Measure the chest expansion using a measuring tape.

PERCUSSION:

- Now percuss all intercostal spaces anteriorly and laterally. Mark upper border of liver on the right.

AUSCULTATION:

- Auscultate lung fields and check vocal resonance.

EXAMINATION OF BACK OF CHEST:

- Now ask the patient to sit on a chair and examine the back of the chest.
- Inspect the back for scoliosis, kyphosis, bulging or flattening.
- Palpate the chest for tenderness.
- Compare chest movements of both sides.
- Percuss the apices and back of the chest.
- Auscultate the intercostal spaces of back and check vocal resonance.

Never forget to cover the patient once examination is complete.
Thank the patient and examiner at the end.

1.4.3. ABDOMINAL EXAMINATION

- Ask the patient to lie down and expose the abdomen, lower chest and lower limbs for examination.
- Stand at the foot end side of the bed.
- Check the shape and size of abdomen: normal, scaphoid, distended.
- Note the shape and position of umbilicus: inverted or everted, slit-like, central or pulled up or down.
- Note movements of abdomen with respirations.
- Note any prominent bulge or swelling.
- Ask the patient to cough and observe the hernia orifices.
- Now stand at the right side of the patient and inspect by keeping your eyes at the level of abdominal surface.
- Notice any prominent veins, obvious peristalsis, pulsations or scars. Check the direction of flow of blood in veins by milking with two fingers.
- While standing at the right side, look from above towards both sides of abdomen. Note any bulging of flanks.
- Now auscultate the abdomen for gut sounds. Auscultate for hepatic bruit, splenic rub, renal bruit, etc.
- Auscultation of abdomen is done before palpation and percussion because these may exaggerate the gut sounds and also induce pain which may hinder the rest of examination.

- Now start the palpation of abdomen. First palpate for any gross masses and tenderness.
- Then start palpation of liver. Mark the upper border of liver by percussion in mid-clavicular line.
- Keep your hand in the right lower quadrant of abdomen such that fingers are parallel to the lower border of rib-cage on right and just lateral to rectus muscles. Now ask the patient to take deep breaths. As the patient breaths in, try palpating liver border with the radial margin of your index finger (Note palpation can also be done using tip of fingers of dominant hand). If not palpable, then advance your fingers 1 cm upwards during expiration. Again try palpating liver edge during inspiration. Keep advancing like this until liver edge is finally appreciated. Ask the patient to keep his/ her finger at that point or mark the area in mid-clavicular line. This is the lower border of liver. Confirm the lower border of liver by percussion. The distance between upper and lower border of liver in the mid-clavicular line is the liver span (right lobe).
- Trace the edge of the liver to the left and check for left lobe enlargement. Mark the span of left lobe of liver from the xiphisternum.
- Note whether the edge of liver is sharp or round. Examine surface for smoothness, nodularity, irregularity or cystic masses. Press the liver slightly to check for tenderness. Examine the liver for pulsatility.
- Now keep your hand in right lower quadrant again, this time parallel to the lower border of rib-cage on left. Palpate with same technique as described for liver and appreciate splenic enlargement. If splenic margin is felt, then note the level and measure splenic size. Splenic size is measured along a line drawn between the tip of ninth costal cartilage on the left and right anterior superior iliac spine. Note tenderness, notch of spleen. Percuss to confirm. Do maneuvers to differentiate from kidney enlargement.
- If spleen is not palpable or dubious, then ask the patient to lie on their right side and hook fingers in the left lower costal margin to appreciate an edge. If still not palpable, percuss for dullness in the lower three intercostal spaces. Auscultate for splenic rub.
- Palpate the gall bladder, kidneys, urinary bladder and aorta.
- Now percuss areas of abdomen and then assess for ascites. Palpate for shifting dullness in both flanks. Check for fluid thrill by tapping one side of abdomen.
- In case of abdominal pain, remember to check for signs of appendicitis, peritonitis or cholecystitis according to the clinical picture.

- Do relevant general examination for anemia, jaundice, clubbing, dehydration, edema, signs of chronic liver disease. Never forget to check hernia orifices, genitalia and digital rectal examination.

Never forget to cover the patient once examination is complete.
Thank the patient and examiner at the end.

1.4.4. CARDIOVASCULAR EXAMINATION

- Ask the patient to lie down and expose the precordium.
- Inspect the precordium for any pulsations, bulges, prominent veins or scars.
- Palpate and localize the apex beat. Note the character of apex beat. If any heave/ thrill is found, check whether it is systolic or diastolic.
- Palpate for parasternal heave.
- Palpate second intercostal spaces on either side for palpable heart sounds.
- Auscultate all four areas corresponding to heart valves.
- Listen to heart sounds especially noting timing, presence of any additional sounds like S3, S4 or murmurs. Time murmurs with carotid pulse.
- If a murmur is found check its duration, grade and radiation.
- For examination of murmurs perform maneuvers: changes with respiration, Valsalva, hand-grip, squatting, standing, leg-raise, etc.
- Ask the patient to sit up and lean forward and listen to aortic and pulmonary areas.
- Examine neck veins at 45 degrees.
- Check blood pressure and calculate pulse pressure.
- Examine peripheral pulses for rate, rhythm, character, volume and condition of vessel wall. Check for radio-femoral delay.
- Do relevant examination including examination for anemia, cyanosis, clubbing, jaundice, edema and ascites. Auscultate lung bases for crepts.

1.4.5. NEUROLOGICAL EXAMINATION

Neurological examination consists of:

- Mental state examination
- Motor system examination
- Sensory system examination
- Cranial nerve examination
- Cerebellar examination
- Signs of meningeal irritation
- Signs of root irritation

MENTAL STATE EXAMINATION:

- Check conscious level of the patient.
- If conscious check orientation to time, place and person.
- Check speech for its components: articulation, fluency, repetition. Ask the patient to name different objects held in front of them. Name three unrelated objects and ask the patient to recall them after one minute.

⇨ ***MINI-COG***

It is a simple tool to screen dementia in the elderly and consists of two parts: clock drawing and three-item recall.

Name three objects: Name three unrelated objects and ask the patient repeat them.

Clock drawing: Ask patient to draw a rounded clock with numbers in it. Draw clock-hands to show a particular time, say for example 8:45.

3-item recall: Ask the patient to recall the three items of the first part of the test.

CRANIAL NERVE EXAMINATION:

Olfactory nerve:
- Rule out nasal obstruction then test both nostrils one by one using some pleasant smells (e.g. soap, light perfume).

Optic nerve:
- Visual acuity: Test for far vision by using a Snellen's chart. Test for near vision using Jegger chart or a newspaper or book.
- Color vision: Test for color vision by using Ishihara chart or different colors.
- Field of vision: Check field of vision by using a perimeter or a rough confrontation method.
- Fundoscopy: perform fundoscopy of both eyes.

Oculomotor, trochlear and abducens nerve:
- Check for ptosis, pupil size, direct and consensual light reflexes and accommodation.
- With the patient's eyes illuminated properly, check for extra-ocular movements in all directions.
- Ask patient to notify if he/ she experiences blurred vision.

Trigeminal nerve:
- Examine the motor part by palpating masseter and temporalis during clenching of teeth.
- Check pterygoids by asking patient to open jaw and move jaw laterally against resistance.
- Check jaw jerk.
- Assess touch (using small piece of cotton) and pain (using blunt pin/ toothpick) along the distribution of the ophthalmic (on fore-head), maxillary (on cheeks) and mandibular (around the jawline) divisions.
- Check corneal and conjunctival reflexes.

Facial nerve:
- Ask patient to do different facial movements:
- Close eyes tight while you attempt to open them (check contraction of palpebral fissures)
- Close eyes while examiner checks for Bell's phenomenon (upward deviation of eyeball on attempting to close the affected side)
- Inflate cheeks and then try to deflate these with fingers (notice the weaker side)
- Show teeth
- Whistle
- Look up without moving head (examine wrinkles on fore-head). These are spared in upper motor neuron lesions.
- Check taste sensation by putting drops of different solutions on both sides of tongue (sour, sweet, saltish and bitter)

Vestibulo-cochlear nerve:
- Examine vestibular part by checking for nystagmus.
- Examine cochlear part by using tuning forks.
- Do whisper test: ask patient to close each ear one by one and then whisper something. If the patient fails to hear it properly then

Glossopharyngeal and vagus nerve:
- Ask the patient to open mouth and check gag reflex by touching the posterior wall of pharynx.
- Ask patient to open mouth and say "Ah".
- Check the movements of vocal cords by asking patient to say "EEE".
- Ask the patient to bend head forwards and sideways against resistance (checks sternocleidomastoid).
- Ask patient to shrug shoulders against resistance.

Hypoglossal nerve:
- Inspect tongue for wasting, abnormal movements or fasciculations.
- Ask patient to protrude tongue.

MOTOR SYSTEM EXAMINATION:
- Ask patient to lie down and expose both limbs.
- Compare both sides of the limbs.

- Measure and compare the circumference of muscle bulk of right and left side.
- Tap on the muscle bulk to check for fasciculations.
- Ask patient to relax his/ her joints. Test passive movements around each joint. Compare tone of both sides in this manner.
- Ask patient to perform different movements around all joints of limbs. Grade the power of movements (See Table 1.2).
- Check for biceps, triceps, brachioradialis, knee and ankle jerks. See Table 1.3. for root values.
- Check plantar reflexes.

Table 1.2: GRADES OF POWER	
0	Complete paralysis
1	Flicker of movement
2	Moves limb when gravity is excluded e.g. side-to-side but not against gravity
3	Can lift limbs against gravity but not against resistance
4	Can move limbs against resistance but with sub-normal power
5	Can move limb against resistance with full power

Table 1.3: NERVE ROOT VALUES OF TENDON REFLEXES	
Deep tendon reflexes	**Root values**
Biceps	C5, C6
Triceps	C6, C7, C8
Brachioradialis	C5, C6
Knee	L2, L3, L4
Ankle	S1, S2

NOW DO CEREBELLAR EXAMINATION:
- Check for nystagmus.
- Check for dysdiadochokinesia.
- Check co-ordination of movements using finger-nose and heel-shin tests.
- Check for cerebellar gait: ask patient to walk in a straight line, then turn and come back.
- Do Romberg's test.

SENSORY SYSTEM EXAMINATION:
Test for:
- Pain (using sharp object like tooth pick. Avoid metallic pins)
- Light touch (use q-tips. Use a monofilament to check for diabetic neuropathy)
- Crude touch
- Position sense
- Temperature (use tuning forks run in hot or cold water)
- Cortical senses

Checking pain, light touch, crude touch and temperature:
- Imagine dermatomes on the patient.
- Now touch the patient using the selected tool (e.g. tooth-pick or q-tip) and let them appreciate the sensation.
- Ask the patient to lie down and close their eyes.
- Now check the required sensation in the dermatomal areas.
- Mark in a chart.

Joint position:
- Grasp the sides of great toe at the interphalangeal joint.
- Place your other hand on the lateral and medial aspects of the great toe distal to the interphalangeal joint.
  Flex the toe and tell the patient that it is "down".
  Extend toe (pull it downwards) and tell the patient that it is "up".
- Now ask the patient to close eyes. Move the toe up or down and ask the patient about the position. Record multiple responses.

Vibration sense:
- Take a 128 Hz tuning fork.
- Ask the patient to close eyes.

- Place a vibrating tuning fork on top of the joint.
- Place one of your fingers under the same joint.
- Ask the patient if he/ she can appreciate vibration.
- If the patient does not feel vibrations while your finger feels them, then there is loss of vibration sense.

Two point discrimination:

- Touch the patient simultaneously at two points on the tested area. Ask whether the patient appreciates one point or two points. Record the minimum distance between two points.

Stereognosis:

- Ask the patient to close eyes. Place a coin or a pencil in patient's hands and ask them to identify.

Graphesthesia:

- Ask the patient to close eyes. Write a letter or number on the palm of the patient and ask them to identify.

Extinction:

- Ask the patient to close eyes. Touch them on the leg or trunk on one side of the body, and ask him/ her to point to the area. Now with patient's eyes closed again, touch them in two places on opposite sides of body and ask them to point to the area. Normal patients will point to both areas.

SIGNS OF MENINGEAL IRRITAITON:

Expose both legs and ask the patient to lie supine.

- **Neck rigidity:** Place your fingers under the occipital region and rest your forearms on the chest. Flex the patient's head and try to touch the chin with chest. In case of neck stiffness, flexion of head is not possible and you will feel stiff neck muscles.
- **Kernig's sign:** Keep your left hand on the medial hamstrings of any leg. Now flex that leg at both hip and knee joints. Then extend the knee while keeping thigh flexed. Feel for spasm of hamstrings which limits the extension. This is positive Kernig's sign. The patient may complain of pain in the thigh and may also flex the other lower limb at hip and knee.
- **Brudzinski's neck sign:** It is reflex flexion of legs and thighs on attempting to flex the neck.
- **Jolt test:** Ask the patient to move head from side to side quickly. If the test is positive, the headache will get worse.

SIGNS OF ROOT IRRITATION:

These are suspected on the basis of sensory deficits in a dermatomal pattern and motor abnormalities at a nerve root level.

- **Straight leg raise test/ Lasèque sign/ Lazarević's sign:** Ask the patient to lie down on his or her back. Raise the patient's leg while keeping knee straight. Development of low back pain denotes herniated lumbar disc. Repeating the test on the opposite leg increases sensitivity of the test.
- **Femoral nerve stretch test/ Mackiewicz sign:** Ask the patient to lie prone. Flex the knee to thigh and then extend the hip. Development of pain in anterior thigh denotes disc protrusion in lumbar region.

1.5. FOLLOW-UP NOTES

Notes should be written in **SOAPE** format:
The note should start with date, time, and age and name of patient.

- **S** = subjective complaints of the patient
- = objective description of physical findings, monitoring parameters and recordings of investigations
- **A** = analysis of data with tentative diagnosis
- **P** = plan of management including therapeutics, investigations and consults.
- **E** = education obtained by searching relevant management guidelines, books and literature for academic discussion.

Daily follow-ups of patients should include the following:

- Review of all catheters and remove if no longer needed.
- Assess patients for mobilization (earlier mobilization leads to improved outcomes).

- Assessment for need of DVT prophylaxis, stress ulcer prophylaxis, fall precautions.
- Assessment for nosocomial infections.
- Review of all prescriptions for errors and possible interactions.
- Review of all medicines which are no longer needed.

1.6. PRESCRIPTION WRITING

- Write in block letters.
- Sign all prescriptions.
- Write prescriptions in a predetermined format:
    - (Form of drug) (Generic and brand names) (Dose) (Site of delivery) (Frequency) (Any special instructions)
    - e.g.
    - Cap OMEPRAZOLE 40 mg PO 1 x OD (half hour before meals)
    - Tab ALENDRONIC ACID 70 mg 1 x weekly (in morning, with a full glass of plain water half hour before food in upright position and do not lie down for at least half hour)
- Write all dilutions in the following format:
    - (Form of drug) (Generic and brand names) (Dose) (Dilution) (Site of delivery) (Frequency)(Duration)
    - e.g.
    - Inj MOXIFLOXACIN 400 mg iv 1 x OD (over one hour and do not admix with other drugs or infuse through same tubing simultaneously)
    - Inj POTASSIUM CHLORIDE 20 mEq x 2 ampoules diluted in 1000 ml N/S iv @ 100 ml/hr (ONCE)
- Encircle all insulin doses. Do not write insulin as 4 u. Either write 4 or 4 units. 4 u may be mistakenly read by some as 44 resulting in over-dose.
- Mention STAT in all medicines which need to be given urgently.
- Cross out previous orders. Do not over-write.
- Write date and time.
- Review prescription charts daily.

1.7. DOCUMENTATION

Documentation is of fundamental importance in medicine for following reasons:

- Research purposes
- Medicolegal importance
- Monitoring response
- Notifying medical events
- Education purposes
- Audit of management decisions

2. CRITICAL CARE MEDICINE

2.1. EVALUATION OF CRITICALLY ILL PATIENT

Evaluation of critically ill patients depends mainly on vital signs.
Aside from experience and instinct, there are several early warning scores which can be used to predict critically ill patients and thus may help in timely prevention.

Table 2.1. MODIFIED EARLY WARNING SYSTEM

	3	2	1	0	1	2	3
Respiratory rate		<8		9 – 14	15 – 20	21 – 29	>30
Pulse rate		<40	40 – 50	51 – 100	101 – 110	111 – 129	>129
Systolic blood pressure	<70	71 – 80	81 – 100	101 – 199		>200	
Consciousness (AVPU)	Unresponsive	Responds to pain	Responds to voice	Alert	New agitation Confusion		
Temperature (ºC)		<35	35.1 – 36	36.1 – 38	38.1 – 38.5	>38.6	
Hourly urine for 2 hours	<10 ml/hr	<30 ml/hr	<45 ml/hr				

Score

- 1 – 2 → perform two-hourly observations and inform nurse in charge.
- 3 → perform 1 – 2 hourly observations and inform nurse in charge.
- Deteriorating score must be attended by a doctor.
- ≥4 → perform ½ hourly observations and must inform doctor.

- Management of critically ill patients depends upon resuscitation, stabilization and monitoring. Clinicians should be familiar with their local crash code protocols and should have an understanding of their crash trolley and defibrillator. One should pay attention to circulation, airway and breathing.
- Recognize signs of poor perfusion and developing shock. For this purpose, monitor pulse, blood pressure, urine output, mentation, skin color, temperature, capillary refill and ECG rhythm. If there is poor perfusion, then consider giving fluid boluses provided chest is clear and there is no fluid overload. Once intravascular volume is restored, consider vasopressor therapy. Inotropes should be used for cardiac dysfunction.
- Evaluate whether patient is maintaining his or her airway independently or needs support. Airway support may include simple maneuvers like head-tilt chin-lift or passing oral or nasal airway. Anything obstructing the airways like blood or secretions should be cleared by suction. Bag-valve mask should be used to deliver ventilations. If needed an advanced airway like endotracheal tube should be placed.
- Intensive Care Units are defined as areas of the hospital that look after patients whose conditions are life-threatening and need constant, close monitoring and support from equipment and medications to keep normal body functions going.
- In ICU different monitors can be used to assess patients e.g. pulse oximetry, capnography, invasive blood pressure using arterial catheters, ABGs, pulmonary artery pressure, non-invasive cardiac output and lactate levels.
- There are many scores which can be used to categorize illness severity. This helps in directing resources, level of care and for prognostication. Some of these scores are non-specific e.g. APACHE, SAPS score while others are specific to diseases e.g. Pneumonia Severity Illness (PSI), GRACE, etc.

2.2. CARDIOPULMONARY RESUSCITATION

"Cardiopulmonary resuscitation is a set of techniques used to maintain circulation and ventilation in patient with life-threatening cardiovascular instability in order to sustain vital functions till the causative factor can be corrected or death declared. Recognizing a collapsing patient (no breathing or gasping or pulseless)."

Check carotid pulse in five seconds and not more than ten seconds.
Start chest compressions if pulseless

- Push hard and fast.
- At least 100 compressions per minute.
- Do compressions in cycles of 30 compressions (≤18 seconds) and two breaths.
- Allow complete recoil of chest.
- Place hand correctly in mid-lower chest over sternum.
- Compress to at least 5 cm (2 inches) in depth.
- Rotate compressors every two minutes.
- Minimize interruptions in compressions.
- Maintain high quality CPR (See Table 2.2.).

Give oxygen.
Attach monitor and defibrillator.

- Defibrillators can be manual or automated (AED).
- Remove clothes or clear chest.
- Attach defibrillator pads.
- If shockable rhythm, then deliver shock.
- Clear everyone before shock.
- After shock, immediately resume CPR.

After two minutes (i.e. 5 cycles of compressions-breaths), check for circulation and breathing.
Maintain airway by head-tilt chin-lift or in case of suspected neck trauma.

- Give two breaths by bag-mask device.
- Squeeze the bag for one second to deliver breaths (one second for each breath).
- A proper seal should be made around the face with C and E technique.
- Only one hand should be used to compress bag.
- Hyper-ventilation should be avoided because of chances of gastric insufflation.

If "Return-of-spontaneous-circulation" achieved then keep patient on monitoring and correct H's and T's. (See Table 2.3.)

Table 2.2. CPR QUALITY ASSESSMENT

Visual assessment of adequate compressions
Quantitative wave-form capnography
PETCo2 should not be <10mmHg
Intra-arterial relaxation phase (diastolic) pressure should not be <20mmHg

Table 2.3. REVERSIBLE CAUSES OF CARDIORESPIRATORY COMPROMISE

H's	T's
Hypovolemia	Tension pneumothorax
Hypoxia	Tamponade, cardiac
Hydrogen ion (acidosis)	Toxins
Hypo-/hyper-kalemia	Thrombosis, coronary
Hypothermia	Thrombosis, pulmonary

- If the monitor shows a shockable rhythm (pulseless ventricular tachycardia or ventricular fibrillation) then a biphasic shock of 120 – 200 joules should be administered every two minutes till rhythm is restored. 1 mg of 1:10000 epinephrine should be administered every three to five minutes. Resume compressions immediately after shock. If shockable rhythm persists even after third shock,then anti-arrhythmic drugs should be used e.g. amiodarone 300 mg iv push followed by 150 mg every three to five minutes. Use lidocaine if arrhythmia is refractory to above treatment (1 – 1.5 mg/kg bolus over 2 – 3 minutes repeated as 0.5 – 0.75 mg/kg in 5 – 10 minutes up to 3 mg/kg total).

- If the monitor shows a non-shockable rhythm (pulseless electrical activity or asystole) then continue chest compressions and administer 1 mg of 1:10000 epinephrine every 3 – 5 minutes.

2.3. CIRCULATORY SHOCK

"Shock (or circulatory shock) is defined as a state of inadequate tissue perfusion."

QUICK FACTS: CIRCULATORY SHOCK	
Pathology:	**Inadequate tissue perfusion → compensatory mechanisms like peripheral vasoconstriction, increased heart rate, increased contractility → failure of compensatory mechanisms in later stage → end-organ damage e.g. liver, kidneys, lungs, gut, heart, brain**
Presentation:	**Features of underlying condition** **Non-specifc symptoms: dry mouth, malaise, dizziness on standing, altered level of consciousness, dyspnea** **General signs of shock: tachycardia, hypotension, delayed capillary refill** **Clinical**
Diagnosis:	**Lactate (marker of perfusion)** **Workup for underlying causes**
Treatment:	**Iv fluids and replace blood volume** **Vasopressors in fluid refractory shock** **Inotropes in case of cardiac dysfunction** **Treat underlying cause**

PATHOPHYSIOLOGY:

- Blood pressure (BP) is a product of cardiac output (CO) and systemic vascular resistance (SVR):

$$\boldsymbol{BP = CO \times SVR}$$

- So a decrease in cardiac output or decrease in systemic vascular resistance can lead to a fall in blood pressure. Traditionally a systolic blood pressure <90 mmHg or a mean arterial pressure <60 mmHg is taken as shock. However in practical terms, the state of shock is not defined by any absolute blood pressure but rather by the effect of any particular blood pressure on the organ perfusion. E.g. person with a systolic blood pressure of 80 mmHg may not be in a state of shock whereas a person with a systolic blood pressure greater than 90 mmHg may have severe organ hypo-perfusion.
- Cardiac output in turn is a product of heart rate and stroke volume.

$$\boldsymbol{CO = Heart\ rate\ (HR) \times Stroke\ volume\ (SV)}$$

- Stroke volume of heart is defined as:

$$\boldsymbol{Stroke\ volume = End\ diastolic\ volume\ (EDV) - End\ systolic\ volume\ (ESV)}$$

- A decrease in stroke volume can be compensated by an increase in heart rate. Likewise bradycardia can be compensated by an increase in stroke volume.

$$\boldsymbol{Effective\ blood\ pressure \propto HR \times (EDV - ESV) \times SVR}$$

- SVR is in turn determined by length of vessels, radius of vessels and blood viscosity. Radius of vessels is maintained by neural sympathetic tone and release of catecholamines and physiologic vasoconstrictors. In distributive types of shock, imbalance of vasodilator and vasoconstrictor signals leads to decrease in vascular resistance.

⇨ ***Shock index: It is the heart rate divided by systolic blood pressure. Its value lies in between 0.5 – 0.8. Values >0.8 raise the suspicion of shock. Values ≥1.0 are associated with poor outcomes.***

Table 2.4. CLASSIFICATION AND CAUSES OF SHOCK		
CLASS OF SHOCK	**FEATURES**	**EXAMPLES**
Distributive shock	↓ SVR ↑ CO ↑ CI ↓ CVP ↓ PCWP ↑↓ SVO2 ↓ O2 extraction	Septic shock Anaphylactic shock Endocrine shock: addisonian crisis, hypothyroidism, thyrotoxicosis Neurogenic shock Hepatic failure
Obstructive shock	↑ CVP/ PCWP ↓ CO ↑ SVR	**Right sided (Low LVEDV):** Cardiac tamponade Constrictive pericarditis Pulmonary embolism (massive) Tension pneumothorax **Left sided (High LVEDV):** Aortic stenosis
Hypovolemic shock	↓ CVP ↓ PCWP ↑ SVR ↓ CO ↓ SVO2	Fluid losses: e.g. diarrhea, vomiting, profuse sweating, excessive diuresis, diabetes insipidus, diabetic ketoacidosis, extensive burns Third spacing: pancreatitis, intestinal obstruction Hemorrhage with internal or external blood loss e.g. GI bleed, peri-partum bleed, traumatic injury to major vessels or body cavities, pelvic or thigh hemorrhage, ruptured aortic aneurysm
Cardiogenic shock (can further be divided in to RV or LV dysfunction)	↓ CO ↑ SVR ↔/ ↑ CVP ↑ PCWP (↔/↓ in RV infarction) ↑↓ SVO2 ↑ O2 extraction	Myocardial infarction, unstable angina Myocarditis Cardiomyopathies Arrhythmias Valvular abnormalities e.g. acute mitral regurgitation, ventricular septal perforation Myocardial contusion Severe bradycardia

STAGES OF SHOCK:

1. Compensated/ non-progressive shock: compensatory mechanisms of body help to maintain adequate tissue perfusion.
2. Decompensated/ progressive shock: compensatory mechanisms are over-powered by the mechanisms of shock and person develops full blown symptoms. Flow to vital organs (primarily brain) is maintained at the expense of other organs.
3. Refractory/ irreversible shock: compensatory mechanisms have failed completely and the patient is now in vicious circle of hypoperfusion-organ damage cycle. Generalized cell injury ultimately leads to death.

SYMPTOMS:

- Non-specific symptoms: dry mouth, headache, confusion, weakness, light-headedness, chest pain, dyspnea.

SIGNS:

- Rapid weak thready pulse; tachypnea (rapid shallow); hypothermia (fever is usually present in septic shock)
- Signs of poor end-organ perfusion: low urine output; confusion/ coma; diminished gut motility (evidenced by sluggish gut sounds; cold clammy skin of peripheries (warm in case of initial distributive shock); pale or cyanosed skin; cold mottled skin (livedo reticularis); not passing stools or increased NG aspirate); hypoxia (type IV respiratory failure); coronary ischemia.
- Markers of intravenous volume depletion: low JVP, changes in RA pressure with spontaneous respirations, changes in pulse pressure during positive pressure mechanical ventilation.

INVESTIGATIONS:

- The diagnosis of shock is mainly clinical based on interpretation of vital signs. Diagnosis is supported by CVP or PCWP measurements.
- Blood pressure, pulse, oxygen saturation, urine output, conscious level, CVP and PCWP are monitored.

- Creatinine, LFT's, CBC, PT, INR, blood gases, lactate levels, etc may be needed to assess organ dysfunction and hypoperfusion.
- Other investigations may be performed according to the cause of shock.

MANAGEMENT:

- Treat the underlying cause.
- Intravenous fluids to replace volume losses or to raise CVP/ SVO2.
- Blood transfusion if there is blood loss.
- Inotropes if cardiac dysfunction is present.
- Vasopressors to increase blood pressure after adequate volume replenishment.
- Prevention of organ shutdown by early-goal directed treatments.
- Prevention of acidosis by restoring organ perfusion.
- Organ support therapy as needed: e.g. hemodialysis/ CVVH in case of renal failure.

COMPLICATIONS:

Any organ can be involved in shock related injury but following are most common:

- Hypoxic brain injury
- Acute tubular necrosis
- Acute respiratory distress syndrome
- Myocardial ischemia
- Liver injury (shock liver)
- Mesenteric ischemia
- Trans-gut migration septicemia

⇨ ***Formula to calculate dose of most inotropes***

$$\textit{Rate in ml per hour or microdrops per min} = \frac{\textit{Dose in } \mu g \textit{ per kg per } \min \times \textit{Weight in kg} \times \textit{Volume in ml} \times 60}{1000 \times \textit{strength of drug in mg}}$$

⇨ ***Patients who are on beta-blockers, who have sinus node dysfunction or those who have coronary ischemia of sinus nodal artery may have relative bradycardia instead of tachycardia. Development of paradoxical signs like bradycardia, sweating in a patient with shock heralds refractory phase of shock.***

Table 2.5. DESCRIPTION OF DIFFERENT INOTROPES AND VASOPRESSORS					
Agents	**Receptors**	**Dose (µg/kg/min)**	**Effects**	**Administration**	**Side-effects**
Dopamine 200 mg vial Duration: <10 min	DA (low dose) DA and β1 (high dose) α1 (higher doses)	2 – 20 µg/kg/min 2 – 5 (renal) 5 – 10 (inotrope) >10 (pressor)	Renal and mesenteric vasodilation (low dose) Cardiac inotrope Vasopressor (high dose)	Dilute in D5W, NS, DS, RL but never in NaHCO3	Tachycardia Arrhythmias Nausea Vomiting Headache Gangrene
Dobutamine 250 mg vial Duration: 10 min	β1 >> β2 and α1	2 – 20 µg/kg/min	Increases CO, HR Decreases SVR by vasodilation Does not increase myocardial oxygen demand much.	Dilute in D5W, NS, DS, RL but never in NaHCO3	Tachyarrhythmias Hypertension Eosinophilic myocarditis Angina Nausea
Norepinephrine 4mg vial (as 8 mg norepinephrine tartarate) Duration: 2 min	α1, α2, β1	0.05 – 1.5 (up to 3.0) µg/kg/min	Increases CO, HR Decreases renal perfusion and SVR, variable effect on BP	Dilute in D5W, NS, DS, RL but never in NaHCO3	Bradycardia Hypertension Arrhythmias Anxiety Dyspnea Nausea Vomiting Tremor Gangrene
Epinephrine 1 mg vial (1:1000) 1 mg vial (1:10,000) Duration: 4 hours	α1, α2, β1, β2	0.01 – 0.1 µg/kg/min (2 – 20 µg/min)	Increase CO, HR Decreases renal perfusion and SVR, variable effect on BP Relaxes all smooth muscles	Dilute in D5W, NS but never in NaHCO3	Angina Anxiety Arrhythmias Dyspnea Flushing Tremor Generates lactate so interferes with lactate levels
Phenylephrine 10 mg vial Duration: 15 min	α1	100 – 180 µg increments bolus Then 0.5 – 3 µg/kg/min (or 40 – 60 µg/min)	Increases SVR and BP Decreases CO and renal perfusion	Dilute in D5W	Hypertension Bradycardia Anxiety Pulmonary edema Metabolic acidosis
Isoproterenol 0.2 mg vial Duration: 8 – 50 min	β1, β2	0.5 – 5 µg/min	Increases CO Decreases SVR Variable BP and renal perfusion	Dilute in D5W	Tachycardia Hypertension Dysrhythmias Angina Increases infarct size
Milrinone 10 mg vial Duration: 3 – 5 hours	PDE inhibitor	50 µg iv push then 0.375 – 0.75 µg/kg/min	Positive inotrope Less chronotrope Direct vasodilator	Dilute in NS, ½ NS, D5W	VT/ SVT Hypotension Headache Angina
Vasopressin 20 units vial Half-life: 10 – 20 min	V2 (renal) and V1 (vascular)	0.01 – 0.04 units/min	Vasoconstrictor Stimulates peristalsis Increases SVR Decreases CO	Dilute to 0.1 – 1 unit/ ml with Ns or D5W	Abdominal cramps Allergic reactions Angina Bronchoconstriction Circumoral pallor Diarrhea Nausea
Terlipressin 1 mg vial Duration: 5 – 6 hr	V2 (renal) and V1 (vascular)	1.3 µg/kg/hr Or 1 -2 mg bolus dose repeated after 6 hours	Vasoconstrictor Stimulates peristalsis Increases SVR Decreases CO	For infusion 1 mg diluted in 60 ml D5W or NS	As above

2.3.1. HYPOVOLEMIC SHOCK

"Hypovolemic shock occurs due to inadequate circulating volume leading to tissue hypoperfusion."

QUICK FACTS: HYPOVOLEMIC SHOCK	
Pathology:	**Loss of circulating volume → inadequately tissue perfusion → compensatory mechanisms like peripheral vasoconstriction, increased heart rate, increased contractility → failure of compensatory mechanisms in later stage → end-organ damage e.g. liver, kidneys, lungs, gut, heart, brain**
Presentation:	**Features of underlying condition e.g. diarrhea, hemorrhage** **Nonspecific symptoms of shock** **Increased diastolic pressure, narrow pulse pressure (initially)** **General signs of shock**
Diagnosis:	**Diagnosis is clinical.** **Workup of underlying cause**
Treatment:	**Stop ongoing losses, give iv fluids and replace blood volume, Blood transfusion in case of hemorrhage, Vasopressors if required**

Table 2.6. CLASSIFICATION OF HEMORRHAGIC SHOCK

	I	II	III	IV
Blood loss (%age)	<15%	15 – 30 %	30 – 40 %	>40 %
Blood loss (ml)	<750 ml	750 – 1500 ml	1500 – 2000 ml	>2000 ml
Pulse rate	<100	>100	>120	>140 Thread central pulses
Blood pressure	Normal	Normal Diastolic blood pressure is raised Pulse pressure narrow	Decreased Both systolic and diastolic blood pressures reduced	Decreased Both systolic and diastolic blood pressures reduced
Metabolic acidosis	None	None	Present	Significant
Capillary refill (seconds)	<2	2 – 3	3 – 4	>5
Skin	Warm, pink	Cold, mottled	Cold, mottled, pale	Pale, cyanosed
Respiratory rate	14 – 20	20 – 30	30 – 40	>40
Neurologic status	Normal	Anxious	Confused	Lethargic, comatose
Urine output (ml/hr)	>30 (>0.5 ml/kg/hr)	20 – 30	5 – 15	<5

- It can be hemorrhagic or nonhemorrhagic.

PATHOPHYSIOLOGY:

- Circulatory volume loss leads to → Tachycardia; peripheral vasoconstriction with shunting of blood to vital organs → increased norepinephrine, ADH, renin, angiotensin. Compensatory mechanisms try to maintain shock.

SYMPTOMS:

- Aside from the non-specific symptoms of circulatory shock, the patient may have symptoms of underlying cause. E.g. loose motions, vomiting in case of gastroenteritis; abdmonial pain in case of ruptured abdominal aneurysm; melena in case of upper GI bleed.
- Patients may give history of trauma.

SIGNS:

- Increased diastolic pressure, narrow pulse pressure, increased pulse rate, pale skin, delayed capillary refill.
- Physical examination may reveal signs related to specifc causes of hypovolemic shock e.g. hematoma in thigh, hemothorax in chest trauma, signs of pregnancy and pelvic findings in case of pregnancy-related complications.

INVESTIGATIONS:

- CBC, urea, creatinine, electrolytes, glucose, lactate, PT, APTT, blood gases, urinalysis, pregnancy test.
- Imaging studies in case of trauma or suspected hemorrhage.
- Emergent endoscopy in case of GI bleed
- Blood group and cross match.

MANAGEMENT:

- Assess airway, breathing and circulation.
- Prevent further injury in case of trauma. Secure bleeding, immobilize patients and splint fractures.
- Do physical examination to look for the cause of shock.
- Raise legs of the patient to direct blood-flow to the heart.
- Obtain intravenous access preferably by two large-bore iv lines. If peripheral iv access cannot be obtained then pass central venous line. Intraosseous access can be used if there is failure to obtain iv access.
- Invasive blood pressure should be recorded in patients with severe hemorrhage.
- Give intravenous fluids to restore volume status. Isotonic saline, Ringer's lactate or colloids like dextran, pentastarch, albumin, etc can be used. Carefully restrict fluids in cases of hemorrhage, in which case do blood transfusions as needed. Patients may need FFP's or platelets which not only improve coagulation status but also raise the intravascular volume.
- Use inotropes or vasopressors if fluid resuscitation fails to increase blood pressure or if patient has underlying cardiac dysfunction.
- Use somatostatin/ octreotide/ vasopressin analogues in case of GI bleed. Do emergency endoscopy.

2.3.2. CARDIOGENIC SHOCK

"Cardiogenic shock is a state of tissue hypoperfusion due to cardiac dysfunction (decreased cardiac output) in presence of adequate intravascular volume."

QUICK FACTS: CARDIOGENIC SHOCK	
Pathology	**Inadequate stroke volume → compensatory mechanisms like increased heart rate, increased peripheral resistance → failure of compensatory mechanisms in later stage → end-organ damage e.g. liver, kidneys, lungs, gut, heart, brain**
Presentation	**Features of underlying condition** **Nonspecific symptoms of shock/ heart failure**
Examination	**Increased diastolic pressure (initial), cold peripheries** **General signs of shock** **Features of underlying infection**
Diagnosis	**Diagnosis is clinical.** **Workup of underlying cause**
Treatment	**Iv fluids (careful)** **Vasopressors for hypotension** **Inotropes for tissue hypoperfusion**

Table 2.7. CAUSES OF CARDIOGENIC SHOCK
Acute myocardial infarction with LV dysfunction (80%), ventricular septal perforation, free wall rupture, extensive right ventricular infarction, acute severe mitral regurgitation or cardiac tamponade.
Decompensated valvular heart disease
Myocarditis
Aortic dissection
Massive pulmonary embolism
Arrhythmias
Iatrogenic e.g. calcium channel blocker or beta-blockers overdose, ACE inhibitors or excessive diuretics

PATHOGENESIS:

- LV dysfunction → decreased LV compliance and increased PCWP → decreased or static cardiac output → redistribution of fluid to lungs → pulmonary edema and cardiogenic shock

- RV dysfunction → increased RV-EDP and CVP → increased RV-EDV -> shift of IV septum to left → impaired LV filling → pulmonary edema and decreased cardiac output.

CRITERIA FOR DIAGNOSIS:

1. Sustained hypotension i.e. SBP <80-90 mmHg for >30 minutes or requirement of vasopressors to maintain SBP or drop in MAP 30 mmHg from baseline value.
2. Pulmonary congestion or elevated LV filling pressures (Pulmonary capillary wedge pressure >15 mmHg or LV end-diastolic pressures >18 mmhg or Right ventricular end-diastolic pressure >10-15 mmHg)
3. Signs of impaired organ perfusion with at least one of the following: altered mental status, cold, clammy skin, oliguria or raised serum lactate.
4. Cardiac index is usually <1.8 L/min/m2 (without support) <2.2 L/min/m2 (with support).

Diagnosis is made by pulmonary capillary wedge pressure or Doppler echocardiography.

Table 2.8. KILLIP CLASSIFICATION OF SEVERITY OF HEART FAILURE

Class	Features	Mortality
I	No evidence of congestive heart failure	5.1%
II	Rales, jugular venous distension, or S3	13.6%
III	Pulmonary edema	32.2%
IV	Cardiogenic shock	57.8%

INVESTIGATIONS AND MONITORING:

- Monitor ECG, intake output, oxygen saturation, lactic acid, creatinine, acid-base status.
- Chest radiography for pulmonary congestion.
- Pulmonary capillary wedge pressure monitoring.
- Echocardiography.

MANAGEMENT:

- Diagnosis is mostly clinical but difficult one. Rapid diagnosis of shock and timely treatment of reversible causes is the key to good outcomes.
- Early revascularization using PCI or CABG is done in cases of acute myocardial infarction.
- Administer intravenous fluids if chest is clear.
- Norepinephrine is the vasopressor of first choice if blood pressure is low.
- Dopamine can be used as an alternative but is associated with increased risk of arrhythmias.
- Dobutamine can be given with norepinephrine to improve cardiac contractility.
- Levosimendan or phosphodiesterase inhibitors like milrinone or inamrinone, improve cardiac function, reduce afterload by vasodilatation and do not increase myocardial oxygen demand.
- Cardiac glycosides are relatively contraindicated after myocardial infarction but may be used in patients with atrial fibrillation or flutter or refractory heart failure.
- Intra-aortic balloon pump may be used as a bridge therapy till revascularization especially in mechanical complications.
- Active percutaneous LV assist devices are used in patients who do not respond to above.
- Extra-corporeal life support (ECLS) can relieve heart and lungs part of their workload.
- Provide supportive treatment e.g. mechanical ventilation, DVT prophylaxis, stress ulcer prophylaxis.
- Anti-thrombotic therapy in case of acute coronary syndromes.

⇨ ***Cardiogenic shock is the most common cause of death in patients with acute myocardial infarction.***

⇨ ***Most common cause of cardiogenic shock is acute coronary syndromes.***

2.3.3. SEPSIS AND SEPTIC SHOCK

*"**Sepsis** is a condition of systemic manifestations of infections."*
OR
"It is a life-threatening organ dysfunction due to a dys-regulated host response to infection."
OR
"According to Third International Consensus Definitions of sepsis, it is a suspected or documented infection with an acute increase of ≥2 SOFA points."

*"**Sepsis-induced hypotension** is defined as sepsis with systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or a decline in SBP by >40 mmHg from baseline."*

*"**Septic shock** issepsis-induced hypotension which persists despite adequate fluid resuscitation and requires vasopressor therapy, or blood lactate concentration ≥2 mmol/L. Also defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality."*

*"**Sepsis-induced tissue hypo-perfusion** is defined as infection-induced hypotension, elevated lactate or oliguria."*

QUICK FACTS: SEPTIC SHOCK	
Pathology:	**Generalized vasodilation and decreased cardiac filling → compensatory mechanisms like increased heart rate, increased contractility → failure of compensatory mechanisms in later stage → end-organ damage e.g. liver, kidneys, lungs, gut, heart, brain**
Presentation:	**Features of underlying condition** **Nonspecific symptoms of shock** **Decreased diastolic pressure, tachycardia, warm peripheries (initially), fever** **General signs of shock** **Features of underlying infection**
Diagnosis:	**Diagnosis is clinical.** **Workup of underlying cause**
Treatment:	**Iv fluids and replace fluid deficit** **Vasopressors in fluid refractory shock** **Stress dose steroids**

DIAGNOSTIC CRITERIA:
Previously sepsis was defined as evidence of infection plus systemic inflammatory response syndrome.

PATHOPHYSIOLOGY:

- Infection → activation of host defenses → release of mediators of inflammation e.g. TNF, interleukins→ vasodilatory mediators, increased endothelial permeability and activation of coagulation pathways.
- Cell wall components of bacteria (lipopolysaccharides in gram negative bacteria, peptidoglycan in gram positive and negative bacteria, and lipoteichoic of gram positive bacteria induce pro-inflammatory mediators. Complement activation clears bacteria but at the same time increases cellular damage.
- Generation of NO and activation of ATP-sensitive potassium channels leads to generalized vasodilation → reduced SVR → shock with wide pulse pressure and heart has to work extra hard. Blood is shunted from vital organs to non-vital organs. Global oxygen extraction ratio is decreased.
- Inflammatory mediators cause endothelial injury → microvascular thrombosis and disseminated intravascular coagulation.

Quick SOFA criteria are a set of facts to quickly screen patients who are at increased risk of having severe sepsis (See Table 2.11.).

Table 2.9. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (Bone et al 1992)
Presence of two or more of the following: 1. Temperature >38ºC or <36ºC 2. Heart rate >90 beats/min 3. Respiratory rate >20 breaths/min or paCO2 <32 mmHg 4. Leucocyte count >12,000/mm3 or <4,000/mm3 or >10% immature bands

Table 2.10. CRITERIA FOR IDENTIFICATION OF SEPSIS (Surviving sepsis guidelines 2012)	
General features	Fever (temperature >38. 3ºC) Hypothermia (temperature <36ºC) Heart rate >90/min Tachypnea Altered mental status Significant edema or positive fluid balance (>20 ml/kg over 24 hours) Hyperglycemia (glucose >140 mg/dl in the absence of diabetes)
Inflammatory features	Leucocyte count >12,000/µL Leucocyte count <4000/µL 10% immature leucocytes Raised plasma CRP Raised plasma pro-calcitonin
Hemodynamic features	Systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg or a decline in SBP by >40 mmHg from baseline
Organ dysfunction features	PaO2/FiO2 ratio <300 Urine output <0.5 ml/kg/hr for at least 2 hours Creatinine increase by >0.5 mg/dL Coagulopathy INR >1.5 or aPTT >60 s Ileus Platelet count <100,000/µL Total bilirubin >4 mg/dL
Tissue hypo-perfusion features	Lactate >1 mmol/L Decreased capillary filling or mottling

Table 2.11. QUICK SOFA (qSOFA) CRITERIA
Respiratory rate ≥22 /min Altered mentation Systolic blood pressure ≤100 mmHg
Presence of any two of these is associated with poor outcome in out-of-ICU patient with clinical suspicion of sepsis.

GOALS OF INITIAL RESUSCITATION IN SEPSIS-INDUCED HYPOTENSION (WITHIN FIRST 6 HOURS):

- CVP 8 – 12 mmHg (12 – 15 if mechanically ventilated) → assesses fluid status
- MAP ≥65 mmHg → assesses hemodynamic status
- Urine output ≥0.5 ml/kg/hour → assesses renal function
- Central venous oxygen saturation (superior vena caval) ≥70% OR mixed venous oxygen saturation ≥65% → assesses tissue oxygenation and perfusion.
- Normalize lactate levels if elevated

Lactate clearance can be used to judge response to treatment:

$$\textbf{Lactate clearance} = \frac{\textbf{initial lactate} - \textbf{lactate after 2 hours}}{\textbf{initial lactate}} \times 100$$

Table 2.12. SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT SCORE
(Vincent et al. 2010)

Organ dysfunction variables	SCORES				
	0	**1**	**2**	**3**	**4**
PaO2/FiO2 ratio (to assess respiration)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets per mm3 (to assess coagulation)	≥150,000	<150	<100	<50	<20
Total bilirubin mg/dl (to assess liver function)	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	>12.0
Cardiovascular function Catecholamines given as µg/kg/min for at least one hour	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 Or Dobutamine (any dose)	Dopamine 5.1-15 Or Epinephrine ≤0.1 Or Norepinephrine ≤0.1	Dopamine >15 Or Epinephrine >0.1 Or Norepinephrine >0.1
GCS (to assess CNS function)	15	13 – 14	10 – 12	6 – 9	<6
Creatinine mg/dl (to assess renal function)	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9	>5.0
Urine output ml/day	-	-	-	<500	<200

Table 2.13. CRITERIA FOR SEVERE SEPSIS
(Surviving sepsis guidelines 2012)

- Sepsis induced hypotension
- Raised lactate levels
- Urine output <0.5 ml/kg/hour persisting for more than 2 hours despite adequate fluid challenge
- Acute lung injury with Carrico index or paO2/FiO2 rat<250 (in the absence of pneumonia)
- Acute lung injury with Carrico index <300 (in the presence of pneumonia)
- Serum creatinine >2.0 mg/dl
- Serum bilirubin >2 mg/dl
- Platelet count <100,000 per µl
- Presence of coagulopathy (INR > 1.5)

Table 2.14. SURVIVING SEPSIS GUIDELINES TASKS OR BUNDLES

Complete within one hour:
Measure lactate levels
Obtain blood cultures before administering antibiotics
Give broad-spectrum antibiotics
Give 30 ml/kg cryastalloid for hypotension or lactate ≥4 mmol/L
Apply vasopressors if hypotensive during or after fluid resuscitation

MANAGEMENT:

- Suspect sepsis in all seriously ill patients.
- A quick SOFA (qSOFA) score can be used to predict patients with likely sepsis.
- Send cultures (blood cultures and cultures from suspected source) preferably before starting antibiotics. However do not delay antibiotic therapy for more than 45 minutes.
- Obtain at least two sets of blood cultures (one percutaneously and one through each vascular access device).
- Do imaging studies to localize source of infection.
- Assess airway. Initiate supplemental oxygen.
- Initiate empiric antibiotics against all likely pathogens that have good penetration in to the tissue which is source of infection.
- Assess antimicrobials daily for de-escalation. Do not administer early combination therapy for more than 3 – 5 days. Total duration of therapy should be 7 – 10 days depending on the infection.
- Use procalcitonin or CRP to assist in discontinuing antimicrobials in patients who later appear not to have infection.

- Initiate antivirals as early as possible in cases of suspected viral etiology.
- Control source of infection emergently e.g. drainage of abscesses, removal of infected catheters.
- Take precautions to reduce risk of nosocomial infections. Maintain patient hygiene.
- Administer crystalloids at least 30 ml/kg initially as fluid challenge. Improvement is based on change in pulse pressure, stroke volume variation, arterial pressure and heart rate. Fluids are best given as 500 – 1000 ml boluses. If needed colloids (5 – 25% albumin), is given as 300 – 500 ml boluses.
- If fluid therapy fails to maintain blood pressure, or patient is already in fluid overload, then administer vasopressors to keep MAP ≥65 mmHg.
- Norepinephrine is the drug of first choice.
- Epinephrine is added if a second agent is needed.
- Vasopressin 0.03 units/min can be added to norepinephrine either to increase MAP or to decrease dose.
- Dopamine can be used as an alternative to norepinephrine only in patients with low risk of arrhythmias and those who have bradycardia. Low dose dopamine should not be used for renal protection.
- Phenylephrine is used only when there are arrhythmias due to norepinephrine, or high cardiac output with low BP, or as salvage therapy.
- Dobutamine can be added in case myocardial dysfunction.
- Intravenous hydrocortisone at a dose of 100 mg Q8H or 50 mg Q6H, if fluid resuscitation fails and to decrease vasopressor doses. Doses more than 300 mg/day are harmful.
- In anemic patients (in the absence of myocardial ischemia or acute hemorrhage), transfuse to a target of 7.0 – 9.0 g/dl.
- Do not transfuse FFPs to correct deranged PT and APTT, if there are no signs of active bleeding.
- Platelets should be transfused if platelet count is <10,000/mm3 (in the absence of bleeding) OR <20,000/mm3 (with high risk of bleeding) OR <50,000/mm3 (in active bleeding, surgery or invasive procedures).
- Mechanical ventilation for sepsis-induced ARDS should use low tidal volumes with high positive end-expiratory pressures (PEEP).
- Insulin (preferably infusion) should be used if more than two glucose readings >180 mg/dl are obtained. Titrate insulin dose to maintain sugars in between 140 – 180 mg/dl. Monitor 1 – 2 hourly till sugar readings are stable, then monitor four hourly.
- Do not use sodium bicarbonate to correct acidosis or to decrease vasopressor dose, if pH is ≥7.15.
- Give prophylaxis against DVT and stress ulcers.
- Start with low dose feeding (enteral or parenteral) and gradually build up as tolerated.

2.4. HYPOXIA AND RESPIRATORY FAILURE

"Hypoxia is decreased oxygen in tissues."
"Hypoxemia is decreased oxygen concentration in blood."

- Hypoxia may be localized (e.g. arterial thrombosis) or generalized (e.g. anemia).
- Hypoxic hypoxia = hypoxia due to decreased partial pressure of oxygen in inhaled air
- Anemic hypoxia = hypoxia due to decreased hemoglobin
- Ischemic hypoxia = hypoxia due to lack of blood flow
- Histotoxic hypoxia = hypoxia due to inability of tissues to transport

2.4.1. ARTERIAL OXYGEN TENSION (PaO2)

- Expected arterial oxygen tension at any age is calculated by the following formula:

$$\boldsymbol{Expected\ PaO2\ = 105\ -\ \frac{Age\ in\ years}{2}}$$

- PaO_2 can be checked in arterial blood gas analysis. A PaO2 less than expected for age means hypoxemia. It may or may not be associated with a decrease in oxygen saturation.

Table 2.15. CAUSES OF ALTERED PaO2 IN ABGs

CAUSES OF PaO_2 LESS THAN EXPECTED	CAUSES OF PaO_2 MORE THAN EXPECTED
False hypoxia due to sample not being cooled immediately	Patient on more than required oxygenation (more FiO_2, more CPAP, more EPAP, more PEEP)
True hypoxia	Sample processed with air bubble (artifact)

2.4.2. OXYGEN SATURATION (SaO2)

- It is the percentage of hemoglobin binding sites in blood occupied by oxygen.
- Pulse oximeter is used to measure oxygen saturation. It gives falsely increased results in case of methemoglobinemia and carboxyhemoglobin. Co-oximeter does not give these false results.

2.4.3. FRACTION OF INSPIRED OXYGEN (FiO2)

- It is the fraction of oxygen in the inspired mixture and is expressed as a percentage.
- e.g. FiO_2 of air is 21% or 0.21
- The FiO_2 of inspired air can be roughly calculated as:

$$\boldsymbol{FiO2 = 0.21 + (0.04 \times Oxygen\ flow\ in\ l/min)}$$

2.4.4. PF RATIO/ CARRICO INDEX (PaO2:FiO2 RATIO)

- It is the amount of FiO_2 to raise blood oxygen to a certain PaO_2 and denotes the need for oxygen. Its normal value is more than 500.

2.4.5. OXYGEN CONTENT

- It is the total amount of oxygen carried in blood.

$$\boldsymbol{Oxygen\ content\ = Dissolved\ oxygen\ + Hemoglobin\ bound\ oxygen}$$

OR

$$\boldsymbol{Oxygen\ content\ = (0.003 \times PaO2) + (1.36 \times Hemoglobin \times \%SaO2)}$$

2.4.6. OXYGEN DELIVERED

- It is the amount of oxygen delivered to tissues.
- It is of value in differentiating distributive shock in sepsis from cardiogenic shock.

$$\boldsymbol{Oxygen\ delivered = arterial\ oxygen\ content - venous\ oxygen\ content}$$

Table 2.16. ALGORITHMIC APPROACH TO HYPOXEMIA

P_aCO_2 not elevated	Normal A-a gradient	Low F_iO_2 (low inspired air)	**Hypoxia**	High altitude Deep sea diving Airway obstruction Foreign body
	Elevated A-a gradient	Improves with supplemental oxygen	**V/Q mismatch**	Acute pulmonary edema Pulmonary embolism Pulmonary hypertension Asthma COPD
		Does not improve with supplemental oxygen	**Shunt**	Pneumonia ARDS Sepsis Hepatopulmonary syndrome Pulmonary AVM Congenital heart disease
P_aCO_2 elevated	Normal A-a gradient		**Hypoventilation alone**	See list of causes of respiratory acidosis
	Elevated A-a gradient	Improves with supplemental oxygen	**Hypoventilation + V/Q mismatch**	-
		Does not improve with supplemental oxygen	**Hypoventilation + Shunt**	-

2.4.7. ALVEOLAR-ARTERIAL GRADIENT (A-a GRADIENT)

Alveolar arterial gradient is a measure of difference between partial pressures of oxygen in alveoli and arteries. It represents the driving pressures needed for diffusion of oxygen.

$$\boldsymbol{Expected\ Alveolar - arterial\ (A-a)\ gradient = 4 + \frac{Age\ in\ years}{4}}$$

OR

$$\boldsymbol{Expected\ A-a\ gradient = 2.5 + (Age\ in\ years \times 0.21)}$$

$$\boldsymbol{Calculated\ A-a\ gradient = PAO2 - PaO2}$$

P_AO_2 = Alveolar oxygen tension in mmHg which can further be calculated by

$$\boldsymbol{PAO2 = [FiO2 \times (760 - 47)] - \left\{\frac{PaCO2}{0.8}\right\}}$$

$$\boldsymbol{PAO2 = [FiO2 \times 713] - \left\{\frac{PaCO2}{0.8}\right\}}$$

2.4.8. RESPIRATORY FAILURE

"It is the failure of respiratory system to maintain oxygenation or carbon dioxide elimination functions."
It can be divided into two broad categories:

1. Hypoxemic respiratory failure
2. Hyperbaric respiratory failure

Table 2.17. CAUSES OF HYPOXEMIC AND HYPERBARIC RESPIRATORY FAILURE	
CAUSES OF HYPOXEMIC RESPIRATORY FAILURE	
Low inspired FiO2	High altitude, foreign body
Diffusion abnormality	Pulmonary alveolar proteinosis, interstitial lung disease
Hypoventilation	Respiratory exhaustion, opioid overdose
Ventilation-perfusion mismatch (V/Q mismatch)	Pulmonary embolus, pulmonary hypertension, COPD, asthma
Shunt	ARDS, pneumonia, pulmonary AVM, congenital heart disease, PFO with right-to-left flow
CAUSES OF HYPERCARBIC RESPIRATORY FAILURE	
Hypoventilation	See causes of respiratory acidosis

Table 2.18. TYPES OF RESPIRATORY FAILURE	
Type of respiratory failure	**Definition and examples**
Hypoxemic or type 1 respiratory failure	Failure to maintain oxygen saturation ≥90% despite inspired oxygen fraction of >60%. **Old definition:** arterial oxygen tension (PaO_2) <60 mmHg with a normal or low arterial carbon dioxide tension ($PaCO_2$).
Hypercarbic or type 2 respiratory failure	Failure of body to maintain pH≥7.30 in case of respiratory acidosis **Old definition:** $PaCO_2$>50 mmHg.
Type 3 respiratory failure	It is also known as peri-operative respiratory failure. It occurs due to atelectasis and insufficiency of abdominal muscles to support respiration e.g. post-laparotomy, gross ascites, morbid obesity.
Type 4 respiratory failure	Failure of respiration in the presence of shock e.g. cardiogenic, septic or hypovolemic shock. Patient has to be intubated and ventilated.

2.4.9. MANAGEMENT OF HYPOXEMIA/ RESPIRATORY FAILURE

- Keep head-end of bed propped up.
- Secure the airway, if patient is unable maintain their airway.
- Give oxygen to target oxygen saturation >90%. Keep saturation in between 88 – 92% in case of COPD.
- Non-invasive ventilation if patients require substantial amounts of oxygen, are in respiratory distress or developing respiratory acidosis.
- Invasive mechanical ventilation when indicated.
- Treatment of underlying disease e.g. antibiotics in case of pneumonia, bronchodilators and steroids in case of asthma.

2.5. ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

“”It is a clinical syndrome of rapid-onset dyspnea, hypoxemia and diffuse chest infiltrates leading to respiratory failure.”

QUICK FACTS: ARDS	
Pathology:	**Neutrophil-mediated damage to endothelium → interstitial and alveolar edema and atelectasis → hypoxemia**
Presentation:	**Features of underlying condition** **Dyspnea, fever** **Features of underlying condition or history of exposure** **Tachypnea, signs of respiratory distress**
Diagnosis:	**Meet criteria for ESCIM definition** **ABGs, chest x-ray, CT scan chest, bronchoscopy**
Treatment:	**Only supportive treatment** **Mechanical ventilation with low tidal volume, increased PEEP, inverse ratio ventilation, prone positioning**

PATHOGENESIS:

The disease consists of three phases:

- **Exudative phase:** It occurs 1 – 7 days after lung injury. Neutrophil mediated injury to endothelium → increased alveolar-capillary permeability leading to fluid leakage → interstitial and alveolar edema and atelectasis → V/Q mismatch and shunting → refractory hypoxemia.

- **Proliferative phase:** It occurs 1 – 2 weeks after lung injury. Inflammatory cells → dense fibrous tissue in lungs → decreased lung compliance, diffusion limitation and pulmonary hypertension.
- **Fibrotic phase:** It occurs 2 – 3 weeks after lung injury. Diffuse scarring and fibrosis due to fibrin deposition → decreased lung compliance. Hypoxemia continues.

Table 2.19. ESICM BERLIN DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME
Acute onset (≤1 week) Bilateral opacities PF ratio <300 mmHg with a minimum of 5 cmH20 PEEP or CPAP Not fully explained by cardiac failure or fluid overload in physician's best estimation (perform echo if not clear)

Table 2.20. CAUSES OF ACUTE RESPIRATORY DISTRESS SYNDROME	
DIRECT CAUSES	**INDIRECT CAUSES**
Pneumonia Aspiration Near-drowning syndrome Toxin inhalation Pulmonary contusion	Sepsis Multiple bone fractures Head trauma Raised intracranial pressure Multiple transfusions Burns Pancreatitis Drugs Amniotic fluid embolism

Table 2.21. PAO_2:FIO_2 RATIO AND SEVERITY OF ARDS	
200 – 300 with findings of ARDS	Mild ARDS
100 – 200 with findings of ARDS	Moderate ARDS
<100 with findings of ARDS	Severe ARDS

PRESENTATION:

- Dyspnea; fever; sweating
- Tachypnea; signs of respiratory distress; crackles; cyanosis.

INVESTIGATIONS:

- Arterial blood gases: show hypoxemia or hypercapnia.
- Chest x-ray: shows bilateral homogenous infiltrates
- CT scan chest: shows bilateral widespread air-space opacities in dependant lung portions. Pulmonary capillary wedge pressure: PCWP ≤18 mm Hg is usually seen in ARDS.
- Broncho-alveolar lavage: a high neutrophil count and lavage-serum protein ratio >0.7 are characteristic of ARDS.

MANAGEMENT:

- Give oxygen as needed.
- Use low tidal volume ventilation (6 ml/kg) with low volume ventilation protocols. Maintain minute ventilation by increasing respiratory rate.
- Use PEEP to prevent lung collapse at the end of expiration.
- Prone positioning ventilation may be used.
- Maintain fluid balance. Pulmonary edema in ARDS is exudative in nature and diuretics have no survival benefit. Diuretics can be used to reduce volume overload.
- Steroids have no role in the initial stages of disease. Steroids should be given in the start of third phase of disease.

⇨ ***Chest x-ray cannot reliably differentiate ARDS from acute pulmonary edema and bilateral pneumonia.***

2.6. OXYGEN DELIVERY DEVICES

Table 2.22. OXYGEN DELIVERY DEVICES	
LOW FLOW DEVICES	**HIGH FLOW DEVICES**
Nasal prongs Simple face masks	Venturi mask Non-rebreather mask Oxyhood Oxygen tent Face tent

2.6.1. NASAL PRONGS

- Low-flow oxygen device
- **Advantages:** Patient can eat, drink and talk.
- **Disadvantages:** cannot be used in epistaxis, nasal injury or obstruction; exact FiO2 cannot be determined.
- **Flow rates and FiO2:** can supply up to 5 litres of oxygen.

2.6.2. SIMPLE FACE MASKS

- **Advantages:** Can give up to 10 l/min of oxygen
- **Disadvantages:** Patient cannot eat, drink or talk. Some patients experience anxiety and discomfort especially claustrophobic ones.
- **Flow rates and FiO2:** up to 10 l/min

2.6.3. VENTURI MASKS

- High-flow oxygen device
- **Advantages:** Precise delivery of oxygen in COPD patients (changing inspiratory pattern does not affect the flow of oxygen and Bernoulli's principle guarantees precise concentration of oxygen)
- Disadvantages:
- **Flow rates and FiO2:** depends on the valve

Table 2.23. DIFFERENT TYPES OF VENTURI MASK VALVES		
Color code	**Oxygen flow (l/min)**	**FiO2**
Blue	2	24%
White	4	28%
Orange	6	31%
Yellow	8	35%
Red	10	40%
Green	15	60%

2.6.4. NON-REBREATHING MASKS

- **Advantages:** One-way valve allows high oxygen flow
- **Disadvantages:** cannot be used in oral injuries, claustrophobia, upper airway obstruction
- **Flow rates and FiO2:** 60 – 80%

2.6.5. HIGH FLOW NASAL CANNULA

- **Advantages:** FiO2 from 21% to 100%; Can generate PEEP
- **Disadvantages:** PEEP drops when mouth is open; cannot be used in epistaxis, nasal obstruction and injury
- **Flow rates and FiO2:** 21% - 100%

2.7. NON-INVASIVE VENTILATION (NIV)

"It is a ventilation modality that supports breathing without the need for intubation or surgical airway."

Classical NIV is used to deliver continuous *positive* airway pressure (CPAP).
It usually comes with two modes: CPAP and Bi-level PAP.

- **CPAP** consists of a sustained delivery of positive airway pressure throughout the respiratory cycle. It helps to recruit collapsed alveoli and decreases work of breathing. It also increases the diffusion of oxygen.
- **Bi-level PAP** consists of differing inspiratory and expiratory CPAP pressures which facilitate chest wall movement and thus ventilation. Expiratory CPAP (EPAP) improves oxygenation. Pressure support (i.e. the difference between IPAP and EPAP helps improve ventilation and removal of carbon dioxide).
    - **S mode:** spontaneous mode in which device assists each spontaneous breath.
    - **T mode:** timed mandatory breaths are given according to set respiratory rate.
    - **S/T mode:** spontaneous timed mode in which spontaneous breaths are assisted and timed mandatory breaths are delivered.

Table 2.24. INDICATIONS AND CONTRAINDICATIONS FOR NON-INVASIVE VENTILATION

INDICATIONS FOR NON-INVASIVE VENTILATION
COPD exacerbation
Acute pulmonary edema
Bilateral pneumonia
After extubation to prevent re-intubation
Hypercarbic respiratory failure in neuromuscular disorders and chest wall diseases
Obstructive sleep apnea syndrome
Patients with DNR/DNI status
CONTRAINDICATIONS TO NON-INVASIVE VENTILATION
Respiratory arrest
Facial trauma/ burns
Recent facial/ upper airway/ upper GI surgery
Fixed obstruction of upper airway
Inability to protect airway
Confusion/ agitation
Vomiting
Bowel obstruction
Uncooperative patients

2.8. INVASIVE VENTILATION (IV)

"It is a ventilation modality that supports breathing with the need for intubation or surgical airway."

Types of breaths:
Respiratory cycles may either be controlled (ventilator parameters are fixed) or assisted (patient's breaths are assisted by the ventilator). These can also be continuous (ventilator gives breaths continuously and does not allow patient breaths in between ventilator breaths) or intermittent (ventilator gives breaths at a set rate and allows patient's breaths in between breaths).

- Volume control: inspiration is initiated by ventilator at a set inspiratory flow rate and is terminated when the set tidal volume is delivered.
- Volume assist: inspiration is initiated by patient at a set inspiratory flow rate and is terminated when the set tidal volume is delivered.
- Pressure control: inspiration is initiated by ventilator with a pressure limit and is terminated when a set inspiratory time is completed.
- Pressure assist: inspiration is initiated by patient with a pressure limit and is terminated when a set inspiratory time is completed.
- Pressure support: inspiration is initiated by patient with a pressure limit and is terminated when a set flow rate is accomplished.

Modes of ventilation:

- Control mode ventilation: ventilator initiated breaths at a fixed rate while ventilator did not sense patient initiated breaths. This has been replaced by continuous mode ventilation.
- Continuous mandatory ventilation (CMV): ventilator initiates breaths at a fixed rate regardless of the patient's effort. In between, spontaneous breaths are not allowed so if a patient is awake, patient-initiated breaths may increase the work of breathing as the patient has to breath on his own. In apneic/ paralyzed patients control mode ventilation, continuous mandatory ventilation and assist control ventilation make no difference. Breaths my be volume controlled (set tidal volume) or pressure controlled (set flow rate). Synchronized mode combines patient efforts with the ventilator.
- Assist control ventilation (ACV): it is the modern form of CMV. Ventilator delivers a preset rate of breaths which can be controlled or assisted. In between, spontaneous breaths are not allowed. Breaths my be volume controlled or pressure controlled.
- Intermittent mandatory ventilation (IMV): breaths are delivered at a preset interval and spontaneous breathing is allowed in between. There is increased risk of barotrauma if ventilator delivers breath when the patient is forcefully exhaling or has already inspired maximally. Synchronized mandatory ventilation is a variation in which patient-initiated breaths and ventilator-initiated breaths are synchronized. There is still an increased work of breathing which can be decreased by adding pressure support. Breaths my be volume controlled or pressure controlled.
- Mandatory minute ventilation: It is a mode of ventilation with a set minute ventilation. If the patients breaths do not meet the target of minute ventilation, then an the ventilator delivers intermittent breaths.
- Pressure support ventilation (PSV): patient initiated breaths are supported by a small amount of pressure during inspiration. Pressure support overcomes the resistance of endotracheal tube and decreases the work of breathing. It is commonly used during weaning.

INITIAL VENTILATOR SETTINGS (FOR VOLUME-CYCLED VENTILATION):

Calculating ideal body weight:
For adult males:

$$\boldsymbol{Ideal\ body\ weight\ =\ \{(height\ in\ inches - 60)\ \times 2.3\}\ + 50}$$

For adult females:

$$\boldsymbol{Ideal\ body\ weight\ =\ \{(height\ in\ inches - 60)\ \times 2.3\}\ + 45.5}$$

Calculate initial tidal volume as 8 ml per kg of ideal body weight.

Target minute ventilation (V_E)
For males: **4 x body surface area**
For females: **3.5 x body surface area**
OR **100 ml/ kg of body weight/ minute**

Body surface area can be calculated by using DuBois formula:

$$\boldsymbol{Body\ surface\ area\ in\ m2\ =\ 0.007184\ \times (height\ in\ cm)^{0.725}\ \times\ (weight\ in\ kg)^{0.425}}$$

Or by using Mosteller method:

$$\boldsymbol{Body\ surface\ area\ in\ m2\ =\ \sqrt{\frac{height\ in\ cm\ \times weight\ in\ kg}{3600}}}$$

- Respiratory rate is selected maintain minute ventilation according to the tidal volume. It is usually between 8 – 12 breaths/min and not more than 35 breaths/min.
- **PEEP settings:**
    - It is a small positive pressure applied at the end of expiration to prevent alveolar collapse. Initial settings are usually between 5 – 7 cm H_2O. PEEP can be increased if FiO_2 of 1.0 (100%) fails to maintain oxygen saturation. It can also reverse atelectasis
- **I:E ratio:**

    - It is the ratio of duration of inspiration to the duration of expiration. It is usually selected as less than 1 e.g. 1:2 or 1:3. In obstructive lung diseases it is selected very low e.g. 1:4.
- Reduce tidal volume by 1 ml/kg every 2 hours until V_T = 6 ml/kg
- Adjust FiO_2 and PEEP to keep paO2 >55 mm Hg or SaO2 >88%.
- If Plateau pressure >30 cm H_2O, decrease V_T by 1 ml/kg till P_{pl} is <30 cm or V_T is 4 ml/kg.
- If pH is 7.15 – 7.30, increase respiratory rate until pH >7.30 or respiratory rate >35 breaths/min.
- If pH is <7.15, increase respiratory rate to 35 breaths/min. If pH is still low then increase V_T by 1 ml/kg till pH is >7.15.

3. INFECTIOUS DISEASES

3.1. PYREXIA OF UNKNOWN ORIGIN (PUO)

Aka fever of unknown origin (FUO)

"Pyrexia of unknown origin is a persistent fever without an obvious source despite appropriate investigations."

DIAGNOSTIC CRITERIA:

Peetersdorf-Beeson criteria:

- Continuous or intermittent fever ≥38.3°C (100.9°F) on several occasions
- Duration more than 3 weeks
- Failure to reach a diagnosis despite one week of inpatient investigations

Durack and Street criteria:

- Continuous or intermittent fever ≥38.3°C (100.9°F) on several occasions
- Duration more than 3 weeks
- Failure to reach a diagnosis despite three outpatient visits, three days of hospitalization or one week of logical and intensive outpatient testing.

CLASSIFICATION OF PUO:

1. Classical: classical PUO
2. Nosocomial: PUO in patients hospitalized for ≥24 hours who were afebrile on admission
3. Neutropenic: PUO in patients with an absolute neutrophil count of ≤500/ mm3
4. HIV-associated: PUO in a patient with confirmed HIV infection

Table 3.1. CLASSIFICATION OF PUO WITH EXAMPLES

Classical	Infectious	Abscesses e.g. abdominal, pelvic, dental, Bacterial infections: tuberculosis, osteomyelitis, endocarditis, sinusitis, prostatitis, Lyme disease, cat-scratch disease, brucellosis, malaria, toxoplasmosis, typhoid fever Viral infections: HIV/ AIDS, cytomegalovirus, EBV infection, Fungal infections Parasitic infections
	Neoplastic	Leukemias, lymphomas, renal cell carcinoma, colorectal carcinoma, hepatocellular carcinoma, pancreatic carcinoma, myelodysplastic syndromes, sarcomas, metastases
	Inflammatory	Rheumatoid arthritis, SLE, polymyalgia rheumatic, Adult Still's disease, polyarteritis nodosa, Reiter's syndrome, inflammatory bowel disease Rheumatic fever Vasculitis e.g. temporal arteritis
	Miscellaneous	Drug-induced fever (salicylates, sulfonamides, barbiturates, antihistamines, penicillin, erythromycin, nitrofurantoin, isoniazid, methyldopa, phenytoin, procainamide) Factitious fever, DVT, chronic hepatitis, sarcoidosis
	Undiagnosed	
Nosocomial		Drug-induced fever Clostridium difficile enterocolitis Septic thrombophlebitis Pulmonary embolism Sinusitis (nasogastric tube associated)
Neutropenic		Opportunistic bacterial infections Candidiasis, aspergillosis, Herpes virus
HIV-associated	Infectious	CMV, Mycobacterium avium-intracellulare, Pneumocystis carinii, coccidiomycosis
	Non-infectious	Kaposi's sarcoma, Lymphoma, drug-induced fever

MANAGEMENT:

- Take thorough history and do complete physical examination to localize a source and then order specific investigations.
- Confirm and document fever by taking rectal temperature. Note the pattern of fever and any associated localizing symptoms or signs.

- If the findings can be localized, then send relevant diagnostic tests.
- Do CBC with differential counts, ESR, CRP, urinalysis, LFT's, muscle enzymes, PPD, control skin tests, urea, creatinine, electrolytes, calcium, acute and convalescent serum samples. Perform blood, urine, sputum and fluid cultures as appropriate.
- Do chest x-ray.
- Assign to the most likely category of differentials and perform specialized workup.
- Investigations may include VDRL, HIV serology, urine for AFB, CMV, EBV, ANA, RF, peripheral smear, SPEP, ASOT, ultrasound, mammography, CT scan of brain/ chest/ abdomen/ pelvis with contrast, MRI brain, nuclear medicine scanning, relevant biopsy, etc.

Table 3.2. CAUSES OF PYREXIA OF UNKNOWN
Infections (30 – 40%)
Neoplasms (20 – 30 %)
Connective tissue disorders (10 – 20 %
Miscellaneous (15 – 20%)
Unknown (10%)

⇨ ***Prolonged PUO is associated more with neoplasms and factitious fever rather than infections.***
⇨ ***Prolonged PUO without systemic symptoms and weight loss is associated with a benign course.***
⇨ ***Most common cause of PUO lasting >6 months is "NO FEVER".***
⇨ ***Most common rheumatologic cause of PUO is adult Still's disease.***

3.2. HEALTH-CARE ASSOCIATED INFECTIONS (HAIs)

Aka nosocomial infections

About 6% of hospitalized patients acquire an infection in the hospital.
These include:

- Hospital-care associated pneumonia HCAP)
- Hospital acquired or nosocomial pneumonia (HAP) – **2ND MOST COMMON HAI**
- Ventilator-associated pneumonia (VAP)
- Catheter associated urinary tract infection (CaUTI) – **MOST COMMON HAI**
- Cannula associated infections
- Central line associated blood stream infections (CLABSI)
- Hospital onset MRSA bacteremia
- Surgical site infections

PREVENTION STRATEGIES:

- Ensure proper indication of every procedure.
- Perform hand hygiene before and after procedures.
- Only trained persons should perform the procedures.
- Use gloves, gown, cap, mask and sterile drapes for passing central lines.
- Remove catheters and central lines as soon as possible.
- Change cannulas frequently.

3.3. BITE-ASSOCIATED INFECTIONS

- **Human bites:** Streptococci, Staphylococci, Enterococci, Corynebacteria, Eikenella corrodens, anerobes (Prevotella, Peptostreptococcus, Porphyromonas, Bacteroides, Fusobacterium, etc.)
- **Dog bites:** Pasteurella, Staphylococci, Streptococci, Capnocytophaga canimorsus, anerobes (Porphyromonas, Bacteroides, Fusobacterium, etc.), rabies virus
- **Cat bites:** Streptococci, Staphylococci, Moraxella, Pasteurella, Bartonella henslae
- **Rat bites:** Spirillum minus, Streptobacillus moniliformis,
- **Snake bites:** Staphylococcus aureus, E. coli, etc.

MANAGEMENT:

- Tetanus prophylaxis should be given in all patients.

- Rabies prophylaxis should be given in all bites capable of transmitting rabies.
- Antibiotic prophylaxis is recommended for most bites e.g. AMOXICILLIN/CLAVULANATE or AMPICILLIN/SULBACTAM for infected human bites.

3.4. SEXUALLY TRANSMITTED INFECTIONS (STIs)

"These are infections which are transmitted from person to person through unprotected sex or genital contact."

These include:

1. Chlamydia
2. Genital warts
3. Genital herpes
4. Gonorrhea
5. Syphillis
6. Trichomoniasis
7. Pubic lice
8. Scabies
9. HIV

SIGNIFICANCE OF STIS:

- Many STIs are clinically silent but still can be transmitted to another person.
- Herpes and syphilis increase the risk of acquiring HIV infection.
- Some STIs can be transmitted from mother to child resulting in stillbirth, neonatal death, low-birth-weight, prematurity and neonatal infections.
- Gonorrhea and chlamydia are among the commonest and preventable causes of infertility.
- HPV infection is associated with development of cervical cancer.

⇨ ***Chlamydia is the most common sexually transmitted infection.***

3.5. VIRAL INFECTIONS

Table 3.3. CLASSIFICATION OF MEDICALLY IMPORTANT VIRUSES	
RNA VIRUSES	
Orthomyxoviruses	Influenza viruses A, B and C
Paramyxoviruses	Respiratory syncytial virus, parainfluenza virus, mumps, rubeola (measles)
Togaviruses	Rubella virus, chikungunya virus
Coronaviruses	Coronavirus
Rhabdoviruses	Rabies virus
Filoviruses	Ebola virus, Marburg virus
Picornaviruses	Hepatitis A virus, poliovirus, Coxsackie virus, echovirus, enterovirus, rhinovirus
Caliciviruses	Norwalk agent, hepatitis E virus
Flaviviruses	Yellow fever virus, dengue virus, hepatitis C virus, West Nile virus, Zika virus
Bunyaviruses	Hantavirus
Arenaviruses	Lymphocytic choriomeningitis, lassa fever virus
Reoviruses	Rotavirus, reovirus
Retroviruses	Human T-cell lymphotropic virus, human immunodeficiency virus
DNA VIRUSES	
Hepadnaviruses	Hepatitis B virus
Parvoviruses	Parvovirus B19
Papoviruses	HPV, JC virus, BK virus
Adenoviruses	Human adenovirus
Herpesviruses	HSV 1 and 2, Varicella-zoster virus, Epstein-Barr virus, Cytomegalovirus, human herpes viruses 6 and 7, Kaposi's sarcoma associated herpes virus
Poxviruses	Smallpox virus, molluscum contagiosum

Table 3.4. COMMON RESPIRATORY VIRUSES AND THEIR MANIFESTATIONS			
VIRUS NAME	**VIRUS CHARACTERISTICS**	**CLINICAL MANIFESTATIONS**	**MANAGEMENT**
Parainfluenza virus	Enveloped single-stranded RNA virus of Paramyxoviridae	Pharyngitis, common cold, pneumonia Croup (children)	Symptomatic treatment Humidified air inhalation Racemic epinephrine inhalation Glucocorticoids Ribavirin (in immunosuppressed)
Rhinovirus	Non-enveloped single-stranded RNA virus of Picornaviridae	Common cold Acute exacerbations of asthma and COPD Pneumonia (children and immunocompromised)	Symptomatic treatment
Human respiratory syncytial virus (HRSV)	Enveloped single-stranded RNA virus of Paramyxoviridae	Common cold Pneumonia and bronchiolitis (children)	Symptomatic treatment Ventilatory support if needed Aerosolized ribavirin **Palivizumab** (monthly) for prophylaxis in selected patients
Coronavirus	Pleomorphic single-stranded RNA virus of Coronaviridae	Common cold Acute exacerbations of asthma and COPD Pneumonia Bronchiolitis Severe acute respiratory syndrome (SARS) Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	Symptomatic relief SARS: Aggressive supportive care, ribavirin (not established), glucocorticoids (not established)
Human metapneumovirus	Pleomorphic single-stranded RNA virus of Paramyxoviridae	Upper respiratory tract illness Lower tract illness in children, elderly and immunosuppressed	Supportive care
Adenovirus	Double-stranded DNA virus of Adenoviridae	Upper and lower respiratory tract illness Pharyngoconjunctival fever Diarrhea Hemorrhagic cystitis Epidemic keratoconjunctivitis Disseminated disease in transplant recipients	Supportive care Ribavirin and cidofovir in disseminated infection

3.5.1. INFLUENZA

"Influenza is an acute febrile respiratory tract illness with variable systemic manifestations caused by Influenza viruses A, B and C."

QUICK FACTS: INFLUENZA	
Pathology:	**Haemagglutinin helps bind to epithelial cells and neuraminidase help in spread of virions.**
Presentation:	**Symptoms: cough, rhinorrhea, sore-throat, fever, headache, chills, myalgias, red watery eyes** **Signs: fever, tachycardia, pharyngitis, rhinitis, red eyes**
Diagnosis:	**Diagnosis is clinical.** **Reverse transcription PCR; Serology**
Treatment:	**Symptomatic treatment for most.** **Anti-virals: neuraminidase inhibitors (oseltamivir, zanamivir), adamantane agents (amantadine, rimantidine)**

VIRUS CHARACTERISTICS:

- Orthomyxoviridae family of RNA viruses.
- Influenza A virus is sub-classified by the presence of surface hemagglutinin (H) antigen and neuraminidase (N) antigen. Hemagglutinin helps to bind to respiratory epithelial cells and neuraminidase helps in spread of new virions. Antibodies against H antigen provide immunity and antibodies against N antigen limit spread of infection. Influenza virus is genetically labile with high mutation rates and genetic reassortment.

- Antigenic drifts are minor variations in a single strain which cause change in immune response and is responsible for annual epidemics.
- Antigenic shifts are major variations caused by genetic reassortment between different strains which lead to global pandemics.

TRANSMISSION:

- It spreads directly from person to person by respiratory secretions or hand-to-hand contact and indirectly by contact with fomites or inhalation of aerosol particles.

PRESENTATION:

Symptoms:

- Respiratory symptoms: Cough, rhinorrhea, sore-throat, pleuritic chest pain, dyspnea
- Systemic symptoms: Sudden onset of fever, headache (usually frontal or retro-orbital), chills, myalgias and malaise along with
- Others: red watery eyes, photophobia, burning eyes, nausea, vomiting, loose motions
- Post-influenzal asthenia is a fatigue syndrome which persists for weeks after infection.

Signs:

- Fever, tachycardia
- Pharyngitis, rhinitis, red watery eyes
- Fatigued appearance
- Lungs are usually clear

COMPLICATIONS:

- Primary influenza pneumonia; secondary bacterial pneumonia; Reye's syndrome; myositis; rhabdomyolysis; myoglobinuria
- CNS complications like encephalitis, transverse myelitis, GBS

INVESTIGATIONS:

- Diagnosis is usually clinical
- Reverse transcription PCR of respiratory samples (throat swabs, nasopharyngeal washes or sputum)
- Viral culture
- Serologic testing of acute and convalescent phase samples

MANAGEMENT:

- For uncomplicated influenza: Symptomatic treatment like anti-pyretics, decongestants, etc
- For high risk of complications or for complicated influenza:
    - Antivirals started within two days of onset of symptoms reduce duration of symptoms and signs
    - Neuraminidase inhibitors: OSELTAMIVIR 75 mg PO BID, ZANAMIVIR 10 mg via inhalation BID
    - Adamantane agents: AMANTADINE 100 mg PO BID (lower dose in elderly), RIMANTIDINE 100-200 mg PO BID

PROPHYLAXIS:

- Annual inactivated or live attenuated influenza vaccine is recommended for all adults >6 months of age and especially for at-risk groups.
- Individuals at high risk of complications, who have been exposed are started on antiviral agents and also vaccinated with inactivated vaccine.

Table 3.5. PATIENTS AT RISK FOR COMPLICATED INFLUENZA
• Age> 65 years • Pregnant females • Chronic cardiopulmonary disease • Chronic kidney disease • Infants • Diabetes • Hemoglobinopathies • Immunosuppression

⇨ ***Human respiratory syncytial virus is the most common cause of lower respiratory disease in infants and young children.***

⇨ ***Parainfluenza virus is the second most common cause of lower respiratory disease in infants and young children.***

⇨ ***Parainfluenza virus is the second most common cause of croup (laryngotracheobronchitis).***

3.5.2. MUMPS

QUICK FACTS: MUMPS	
Pathology:	**Virus causes parotitis**
Presentation:	**Prodromal illness → unilateral or bilateral parotid swelling** **Complications: epididymo-orchitis, oophoritis, aseptic meningitis**
Diagnosis:	**Clinical diagnosis** **IF or RT-PCR of throat swab, CSF, urine**
Treatment:	**Supportive care**

VIRUS CHARACTERISTICS:

- Negative-strand nonsegmented RNA virus of Paramyxoviridae
- Humans are the only natural hosts.
- It is transmitted from person-to-person by respiratory secretions and by fomites.

SYMPTOMS AND SIGNS:

- Most of the infections are asymptomatic or with mild respiratory complains.
- Majority of symptomatic patients present with unilateral or bilateral parotid swelling (due to parotitis) which persists for about one week. Patients typically complain of difficulty eating, swallowing and/or talking and earache.
- A prodromal illness of fever, malaise, myalgias, headache and anorexia may precede parotitis.
- Epididymo-orchitis: may develop in 15-30% of cases of post-pubertal males. 10-30% of cases of orchitis are bilateral. Sterility is a dreaded but rare complication. Patients complain of painful, tender and enlarged testes.
- Oophoritis: occurs in about 5% of females and presents as abdominal pain and vomiting.
- Aseptic meningitis: occurs in <10% of patients
- Other manifestations: pancreatitis, myocarditis, thyroiditis, nephritis, arthritis, etc.

INVESTIGATIONS:

- Clinical diagnosis
- Viral antigen or RNA in throat swab, CSF, urine, seminal fluid via immunofluorescence or reverse transcription PCR.
- Serology is of limited value.

MANAGEMENT:

- Disease is self-resolving and needs symptomatic care. Orchitis may need applying cold compresses to scrotum and steroids.
- Preventable by vaccination: MMR (measles-mumps-rubella)

3.5.3. MEASLES

Aka Rubeola, Morbilli, Red measles, First disease

QUICK FACTS: MEASLES	
Pathology:	**Virus infects nasopharyngeal epithelium → regional lymph nodes → viremia →reticuloendothelial cells → second viremia → other organs**
Presentation:	**Prodrome: fever, cough, coryza, conjunctivitis, Koplik's spots Exanthem: maculopapular rash (behind ears → trunk → limbs) Complications: pneumonia, encephalitis, MIBE, SSPE**
Diagnosis:	**Clinical diagnosis + IgM, viral culture and RT-PCR**
Treatment:	**Symptomatic, Vitamin A, Treat secondary infections**

VIRUS CHARACTERISTICS:

- Non-segmented single-stranded negative-sense RNA virus of Paramyxoviridae.
- Incubation period = 10 – 12 days

TRANSMISSION:

- Humans are the only reservoirs.
- It spreads indirectly from person to person by respiratory droplets.

PATHOGENESIS:

- Measles virus infects nasopharyngeal epithelium → invades and spreads to regional lymph nodes → viremia occurs and involves distal reticuloendothelial system → proliferates and second viremia occurs which spreads to other organs

SYMPTOMS AND SIGNS:

- Prodrome (lasts 1 – 3 days):
  - High grade fever, malaise, Cough, Coryza and Conjunctivitis.
  - *Koplik's spots* are bluish-white macules with surrounding erythema which appear on buccal mucosa about 2 days before the characteristic rash.
- Rash of measles is an erythematous, non-pruritic maculopapular rash that begins behind the ears and spreads to trunk and then to limbs involving palms and soles. It appears 2 – 4 days after prodrome or 14 days after exposure. It resolves in 7 – 10 days.

COMPLICATIONS:

- *Giant-cell pneumonitis*
- Secondary bacterial infection of respiratory tract e.g. otitis media.
- *Post-measles encephalitis*: Fever, seizures, neurologic deficits occur two weeks after measles rash.
- *Measles inclusion-body encephalitis (MIBE):* Late complication occurring months to years after initial infection in patients with impaired cell-mediated immunity.
- *Sub-acute sclerosing panencephalitis (SSPE):* Late complication presenting with seizures and progressive neurologic deficits culminating in death.

DIAGNOSIS:

- Diagnosis is clinical. Measles-specific IgM; Viral culture and reverse-transcription PCR analysis.

MANAGEMENT:

- Symptomatic treatment
- Antibiotics for secondary bacterial infections
- Vitamin A for children (>1year of age): two doses of 200,000 IU daily

PREVENTION:

- Two doses of live attenuated vaccine containing measles, mumps and rubella (MMR)
- Immunoglobulins in high-risk individuals within 6 days of exposure.

⇨ ***Koplik's spots are pathognomonic of measles.***
⇨ ***Fifth disease: erythema infectiosum caused by parvovirus B19***
⇨ ***Sixth disease: exanthem subitum caused by human herpes 6 and 7***

3.5.4. RUBELLA

Aka German measles, 3-day measles, Third disease

QUICK FACTS: RUBELLA	
Pathology:	**Rubella infection**
Presentation:	**Low-grade fever, upper respiratory symptoms** **Maculopapular rash** **Occipital and pre-auricular lymphadenopathy** **Congenital: cataracts, sensorineural deafness, PDA, PS**
Diagnosis:	**Rubella IgM**
Treatment:	**Symptomatic**

VIRUS CHARACTERISTICS:

- Single-stranded enveloped RNA virus of Togaviridae.
- Incubation period: 1 – 20 days.

TRANSMISSION:

- It spreads indirectly from person to person by respiratory droplets. Congenital infection occurs via transplacental infection.

PATHOPHYSIOLOGY:

- Virus infects nasopharyngeal epithelium → regional lymph nodes → viremia → reticuloendothelial cells → second viremia → other organs

SYMPTOMS AND SIGNS:

- After an incubation period of fourteen days, patients may develop low-grade fever, malaise, upper respiratory symptoms. Generalized maculopapular rash (similar to measles) lasts ≤3 days. Occipital and post-auricular lymphadenopathy is common.
- Forchheimer spots: petechiae on soft palate
- Arthralgias or arthritis
- Congenital rubella infection: Transmission usually occurs during first trimester of pregnancy and leads to cataracts, sensorineural deafness, thrombocytopenic purpura, patent ductus arteriosus and pulmonary artery stenosis.

INVESTIGATIONS:

- Rubella IgM
- Four-fold rise in Rubella IgG
- Congenital rubella is diagnosed by IgM antibodies or by isolation of virus from throat swabs, urine or CSF, or by IgG titer which does not decline at the expected rate.

MANAGEMENT:

- Symptomatic treatment.
- All pregnant women are screened for Rubella IgG during pre-natal care. If negative they should be vaccinated post-partum. Pregnancy should be avoided for at least 28 days after vaccination.

3.5.5. CHIKUNGUNYA

QUICK FACTS: CHIKUNGUNYA	
Pathology:	**Virus infects antigen presenting cells and fibroblasts.**
Presentation:	**High-grade fever, migratory polyarthritis, maculopapular rash Chronic seronegative polyarthritis**
Diagnosis:	**Clinical diagnosis. Virus culture; PCR; IGM and IgG**
Treatment:	**Acute: Symptomatic, NSAIDs after ruling out dengue For chronic polyarthritis: steroids, MTX, HCQ**

Virus characteristics:

- Single-stranded RNA virus of Togaviridae

Transmission:

- It spreads from person to person by the bite of Aedes mosquitoes.
- Vertical transmission
- Transfusion of infected blood products

Pathophysiology:

- Virus infects antigen presenting cells and also fibroblasts.

Symptoms and signs:

- After an incubation period of 3 – 7 days → an acute febrile illness: high-grade fever with shaking chills, joint pain (migratory, polyarticular, involving small joints, wrists and ankles and sometimes knee and shoulder), joint swelling, headache, muscle pain or rash.
- Erythematous maulopapular rash.
- Disease usually resolves within one week. Joint pain may persist in some patients.
- Seronegative chronic polyarthritis meeting criteria for rheumatoid arthritis can persist after infection.

Investigations:

- Virus culture
- PCR
- ELISA for IgM antibodies (appear after 5 – 7 days) and IgG antibodies

Management:

- Treatment is supportive. Hydrate well.
- Give anti-pyretics and analgesics for fever and joint pains. Aspirin and steroids should not be used. NSAIDs can be used provided dengue is ruled out.
- Prevention: protection from bite of infected mosquitoes, destruction of breeding sites of mosquitoes
- Steroids, methotrexate or hydroxychloroquine for rheumatoid arthritis

⇨ ***Triad of symptoms in chikungunya fever = Fever + Joint involvement + rash***

3.5.6. RABIES

QUICK FACTS: RABIES	
Pathology:	**Virus acquired via bites → travels up through peripheral nerves → encephalitis**
Presentation:	**Pain, itching and paresthesias at the time of bite** **Fever, chills, malaise** **Fasciculations, priapism, seizures** **Encephalitic (agitation, biting, hyperactivity, hydrophobia) or paralytic features** **Coma**
Diagnosis:	**Clinical history** **Skin biopsy of wound** **Corneal scrapings** **Viral culture and PCR of saliva or CSF**
Treatment:	**Before appearance of symptoms: HRIG** **After appearance of symptoms: supportive**

VIRUS CHARACTERISTICS:

- Non-segmented, negative sense, single-stranded RNA virus of enterovirus group of Rhabdoviridae.

TRANSMISSION:

- Virus is transmitted via saliva or in aerosolized secretions especially via bites of rabid animals e.g. dogs, cats, bats, coyotes, foxes, raccoons, skunks, etc.

PATHOPHYSIOLOGY:

- The virus enters the peripheral nerves → travels up to the spinal ganglion → pain or paresthesias → travels up to CNS → causes encephalitis → secreted in highly innervated areas e.g. saliva, cornea, skin.

SYMPTOMS AND SIGNS:

- Incubation period:
  - One to two months period
- Prodromal phase:
  - Pain, itching or paresthesias at the site of bite (pathognomonic).
  - Malaise, fever, fever, chills, headaches, pharyngitis, emesis, anxiety, agitation, etc.
- Acute neurologic phase:
  - Fasciculations, priapism, focal or generalized seizures
  - In encephalitic rabies – episodes of agitation, hyperactivity, confusion and biting behavior which may be triggered by various stimuli. Hydrophobia may be present.
  - In paralytic rabies – no furious episodes, but paralysis develops, starting from the bitten extremity and then spreads to all four limbs.
- Coma phase:
  - Patients develop coma and respiratory arrest.

INVESTIGATIONS:

- It is usually diagnosed on the basis of history. Investigations may reveal following:
- Skin biopsy (usually from the nape of skin) – direct fluorescent antibody staining rabies virus antigen in hair follicle nerve endings
- Direct fluorescent antibody staining of corneal scrapings
- Viral culture and PCR of saliva or CSF.
- Brain biopsy (usually postmortem) – intracytoplasmic inclusion bodies aka Negri bodies

MANAGEMENT:

- Immediately after the bite, flush and wash the wound for 15 minutes with soap water, detergent or povidone-iodine solution.
- Debride the wound if needed and leave the wound open.
- If the animal is caught then it can be observed for 10 days in captivity and observed for signs of rabies. If animal remains healthy then no need for vaccination.

- For previously unvaccinated patients: administer human rabies immunoglobulin (HRIG) 20 IU/kg within 7 days of bite. Administer large part of dose in the wound area and remaining part intragluteally.
- Post-exposure prophylaxis: Administer 1 ml of intra-deltoid Rabies vaccine on days 0, 3, 7 and 14 (an extra dose on day 28 in immuno-compromised patients).
- Always remember to administer HRIG and vaccine on separate limbs.
- For previously vaccinated patients, just two doses on days 0 and 3 are sufficient and HRIG is not needed.
- Pre-exposure prophylaxis is administered to at-risk population as 2 doses of 1 ml cell-culture vaccine intramuscular or intradermal on days 0, 7 and 28.
- Once symptoms develop patients should be admitted in intensive care and be provided supportive care. Survival is extremely rare and no therapy is effective. Steroids are contraindicated.

⇨ ***Milwaukee protocol is an experimental protocol of treatment of symptomatic rabies and consists of: pharmacologically induced coma + ventilator support + antiviral drugs***.

3.5.7. EBOLA VIRUS

"It is a disease caused by species of Ebola virus and leads to disseminated intravascular coagulation, septic shock and multi-organ failure."

QUICK FACTS: EBOLA	
Pathology:	**Infects multiple cells**
Presentation:	**Fever, sore-throat, pharyngitis, myalgias, maculopapular rash, conjunctivitis Expressionless face, DIC, myocarditis, hepatitis, renal failure, pancreatitis, shock**
Diagnosis:	**ELISA for antigens or antibodies**
Treatment:	**Supportive treatment Isolation**

VIRUS CHARACTERISTICS:

- Non-segmented, negative-sense enveloped, single-stranded RNA virus of filovirus family

TRANSMISSION:

- Animal-to-human and human-to-human transmission by direct contact with body fluids

PATHOPHYSIOLOGY:

- Glycoproteins of virus → infection of vast variety of cells → extensive viral replication → inflammatory cytokines → sepsis-like state, liver necrosis, etc

SYMPTOMS AND SIGNS:

- After an incubation period of about 3-8 days symptoms appear.
- Initially patients have fever, sore-throat due to pharyngitis, severe myalgia, maculo-papular rash and bilateral conjunctivitis.
- Later patients develop expressionless face, bleeding due to DIC, myocarditis, hepatitis, renal failure and pancreatitis.
- Death usually occurs due to septic shock.

INVESTIGATIONS:

- CBC: thrombocytopenia, lymphopenia
- Virus isolation
- ELISA for viral antigens or antibodies.

MANAGEMENT:

- It is associated with very high mortality rate.
- Treatment is supportive including early aggressive hydration, blood products, correction of electrolyte derangements.
- Strict barrier isolation and nursing is advised. All secretions must be handled with care.

Table 3.6. COMMON VIRAL HEMORRHAGIC FEVER SYNDROMES

Arenaviruses	Lassa fever
Bunyaviruses	Hantavirus disease
Flaviviruses	Dengue hemorrhagic fever, yellow fever
Filoviruses	Ebola virus disease, Marburg virus disease

3.5.8. POLIOVIRUS

QUICK FACTS: POLIOMYELITIS	
Pathology	**Virus infection → destruction of anterior horn cells**
Presentation	**Abortive polio; Asymptomatic infection; Aseptic meningitis Paralytic polio: gradual asymmetric flaccid paralysis Post-polio syndrome**
Diagnosis	**Virus isolation from throat washings, stool, blood or CSF**
Treatment	**Supportive care**

VIRUS CHARACTERISTICS:

- Non-enveloped single-stranded RNA virus of enterovirus group of Picornaviridae

TRANSMISSION:

- It is transmitted from person-to-person by fecal-oral route and by aerosol droplets.

PATHOPHYSIOLOGY:

- Virus destroys the anterior horn cells of spinal cord resulting in paralysis.

SYMPTOMS AND SIGNS:

- After an incubation period of 3 - 6 days, patients may develop any of the following:
    - Abortive polio: Mild disease manifested by fever, malaise, sore throat, headache and myalgias.
    - Asymptomatic infection: >90% of patients
    - Aseptic meningitis
    - Paralytic polio: severe body pains followed by gradual asymmetrical flaccid paralysis. Weakness is more pronounced proximally and in legs.
    - Post-polio syndrome: Insidious weakness occurring many years after polio.

INVESTIGATIONS:

- CSF: increased pressure, neutrophilic pleocytosis followed by lymphocytic pleocytosis, elevated proteins
- CBC: elevated proteins
- Body fluids (throat washing, stool, blood, CSF) cultures
- PCR

TREATMENT:

- Supportive care
- Dealing with contractures
- Watch for development of respiratory insufficiency

3.5.9. OTHER ENTEROVIRUSES

Enteroviruses are reported to cause multiple diseases in humans namely:

1. Non-specific febrile illnesses
2. Aseptic meningo-encephalitis
3. Bornholm disease or pleurodynia aka Devil's grip
4. Myocarditis
5. Pericarditis
6. Hand-foot-and-mouth disease
7. Hemorrhagic conjunctivitis

3.5.10. ZIKA VIRUS

QUICK FACTS: ZIKA VIRUS	
Pathology:	**Virus infects dendritic cells → replicates → spreads to blood and lymphatics**
Presentation:	**Asymptomatic** **Maculopapular rash, fever, small joint arthralgia, retro-orbital headache, conjunctivitis** **Complications: GBS, congenital malformations**
Diagnosis:	**RT PCR of urine or serum** **IgM ELISA**
Treatment:	**Supportive treatment**

VIRUS CHARACTERISTICS:

- Enveloped single-stranded RNA virus of Flaviviridae.

TRANSMISSION:

- Direct transmission by the bite of Aedes mosquito.
- Sexual transmission
- Transplacental transmission

PATHOPHYSIOLOGY:

- After mosquito bite virus replicates in dendritic cells → spreads to blood and lymphatics

SYMPTOMS AND SIGNS:

- After an incubation period of 3 – 12 days → diffuse fine maculopapular rash (involving palms and soles), fever, arthralgia (involving small joints of hands and feet), retro-orbital headache, conjunctivitis.
- Most patients are asymptomatic.

INVESTIGATIONS:

- Reverse-transcription PCR of urine or serum
- ELISA for IgM

Treatment:

- Most infections are mild and self-limiting.
- If needed treatment is supportive.
- Avoid NSAIDs if dengue fever is not ruled out.

⇨ ***Most feared complications of zika virus infection are Guillain-Barre syndrome and congenital malformations in pregnant females (including microcephaly and ophthalmologic complicaitons).***

3.5.11. DENGUE FEVER

aka Break-bone fever

"Dengue fever is a viral hemorrhagic fever caused by dengue virus and characterized by fever, thrombocytopenia, hemorrhagic and capillary leak manifestations."

QUICK FACTS: DENGUE FEVER	
Pathology:	**Virus infects dendritic cells → migrates to regional lymph nodes → activates humoral and cellular immunity → replicates in macrophages and monocytes**
Presentation:	**Febrile phase: fever, chills, flushed face, headache, retro-orbital pain, photophobia, backache, myalgias, nausea** **Critical phase: no fever or saddle-back fever, hemorrhagic manifestations, capillary leak manifestations** **Recovery phase: recovery, bradycardia** **Complications: hemorrhage, hypotension, liver failure, renal failure, neurological manifestations**
Diagnosis:	**Dengue NS1 antigen, PCR** **Dengue IgM**
Treatment:	**Supportive treatment** **Fluids and hydration** **Avoid aspirin, NSAIDs**

VIRUS CHARACTERISTICS:

- Dengue virus is a flavivirus of flaviviridae family with positive-sense single stranded RNA.
- There are four main serotypes namely DENV-1, -2, -3 and -4.

TRANSMISSION:

- The virus is transmitted by the bite of female Aedes mosquito (Aedes aegypti).

PATHOPHYSIOLOGY:

- After mosquito bite, virus spreads to immature dendritic cells. Then it migrates to regional lymph nodes and activates humoral and cellular immunity. Virus replicates in macrophages and circulating monocytes. Cellular immunity leads to production of various cytokines. Humoral immunity generates anti-platelet antibodies and antibodies which activate complement cascade.
- Homotypic immunity is life-long (to same serotype). Heterotypic immunity lasts few months (against other serotypes).

SYMPTOMS/ SIGNS:

Dengue has an incubation period of 4 – 10 days. Thereafter the course of the disease is divided into three phases.

- Febrile phase:
  - It lasts two to seven days. Symptoms include fever (sharp, high-grade,duration two to seven days), chills, flushed face, headache, retro-bulbar pain on eye movements or eye pressure, rash (typically on third day), photophobia, backache, myalgia, arthralgia, anorexia, altered sensation, constipation, colicky abdominal pain, sore-throat.
  - Hess's tourniquet test may be positive. It is the appearance of petechiae on arm when BP cuff is inflated and left between systolic and diastolic pressures for 5 minutes.
- Critical phase:
  - It is usually of one to two days duration but can be up to seven days long. During this phase, fever subsides or returns as saddle-back fever. Hemorrhagic manifestations develop. In severe cases capillary leakage may develop resulting in edema, ascites, pleural effusion or shock. Signs of severe organ impairment may develop e.g. hepatitis, encephalitis, myocarditis, etc.
- Recovery phase:

- All symptoms resolve during next two to three days in case of uncomplicated dengue. Hypervolemia may develop if fluidsare not decreased judiciously during this phase. Patients usually have bradycardia.
- An erythematous rash may be seen with typical "islands of white in the sea of red" appearance.

INVESTIGATIONS:

- Complete blood count: Leukopenia with neutropenia develops in febrile phase. Platelets start to decline in the critical phase. Mild rise in hematocrit is common due to vomiting and fever but it rises steeply during critical phase due to capillary leak. A rise in hematocrit ≥20% is associated with severe dengue.
- **Liver enzymes:** mild derangements are common.
- **Virus detection:** It is usually done in first 5 days of illness by Dengue NS1 antigen or viral PCR.
- **Serological tests:** Dengue IgM or Dengue IgG antibodies
- **Others:** Hypoproteinemia, hyponatremia, mild albuminuria, coagulopathy, hypocalcemia, etc.

Table 3.7. CLASSIFICATION OF DENGUE FEVER

Dengue fever		**Fever with two of the following:** Headache Retro-orbital pain Myalgia Arthralgia/ bone pain Rash Hemorrhagic manifestations No evidence of plasma leakage	Leukopenia (WBCs ≤5000/mm3) Thrombocytopenia (<150,000/mm3) Rising hematocrit (5-10%) No evidence of plasma loss
Dengue hemorrhagic fever Grade I		Fever and hemorrhagic manifestations including positive Hess test and evidence of plasma leakage	Platelets <100,000/mm3 Hematocrit rise ≥20%
Dengue hemorrhagic fever Grade II		Grade I plus spontaneous bleeding	Platelets <100,000/mm3 Hematocrit rise ≥20%
Dengue hemorrhagic fever Grade III		Grade I or II plus signs of circulatory failure (tachycardia, cold extremities, delayed capillary refill, weak pulse, narrow pulse pressure, lethargy or restlessness, hypotension	Platelets <100,000/mm3 Hematocrit rise ≥20%
IV	**Dengue hemorrhagic fever Grade IV/ Dengue shock syndrome**	Grade III plus severe shock	Platelets <100,000/mm3 Hematocrit rise ≥20%
	Expended dengue syndrome	Neurologic, gastrointestinal, hepatic, renal, cardiac, respiratory, lymphoreticular or psychiatric manifestations	

MANAGEMENT:

- Management is mainly supportive and involves triage in to dengue without warning signs (group A), dengue with warning signs (group B) and severe dengue (group C).
- Group A patients are sent home and should be advised bed rest, adequate fluid intake, PARACETAMOL as antipyretic and counseled to return if warning signs develop.
- Group B patients undergo intensive monitoring of urine output and hematological parameters, and robust fluid therapy.
- Group C patients are resuscitated aggressively with crystalloids or colloids and if needed blood transfusion.

⇨ ***Dengue is the most rapidly spreading mosquito-borne viral disease in the world.***

⇨ ***Leukopenia is the earliest laboratory abnormality in dengue fever.***

⇨ ***DON'Ts of dengue management: don't use corticosteroids, don't give platelet transfusions for a low platelet count, don't give half normal (0.45%) saline, don'tassume that intravenous fluids are necessary.***

3.5.12. HUMAN IMMUNODEFICIENCY VIRUS INFECTION (HIV)

Aka HIV disease

"It is a state of progressive immunodeficiency induced by HIV-1 or HIV-2 viruses."

QUICK FACTS: HIV	
Pathology:	**Virus infects CD4 helper T cells → decreases CD4 counts → dysregulated B-cell antibody production → defective cell-mediated immunity**
Presentation:	**Acute seroconversion: flu-like illness, maculopapular rash** **Asymptomatic infection: persistent generalized lymphadenopathy** **AIDS related complex: minor opportunistic infections** **AIDS: AIDS defining illnesses**
Diagnosis:	**ELISA HIV1 and 2, HIV p24 antigen** **Western blot** **Viral load**
Treatment:	**HAART**

VIRUS CHARACTERISTICS:

- Enveloped single-stranded positive sense RNA retrovirus

TRANSMISSION:

- Unprotected sexual contact – vaginal and anal intercourse, oral sex
- Percutaenous - shared intravenous drugs
- Mother-to-child – during birth and breastfeeding
- Transfusion of untested blood
- Mucosal contact with infected blood

PATHOPHYSIOLOGY:

- HIV virus infects CCR5 positive CD4 helper T cells → Decrease in CD4 helper T cell counts → Dys-regulated B cell antibody production → defective cell-mediated immunity → opportunistic infections mainly fungal and viral infections.

PRESENTATION:

There are no specific findings of HIV infection itself.
Stages of HIV infection:

1. Acute seroconversion: presents as a flu-like illness with fever, malaise, myalgia, pharyngitis and generalized maculopapular rash approximately 2 – 6 weeks after exposure.
2. Asymptomatic infection: is unremarkable but may have persistent generalized lymphadenopathy which is defined by ≥2 extra-inguinal sites of lymphadenopathy (>1 cm diameter) which persist for ≥3 months.
3. AIDS related complex: is characterized by constitutional symptoms and minor opportunistic infections.
4. AIDS: is presence of AIDS-defining illnesses and usually has a CD4 count of ≤200/ µl. It presents as recurrent severe infections and associated malignancies.

INVESTIGATIONS:

- Screening: ELISA for HIV-1 and HIV-2 antibodies; earlier screening is possible with HIV p24 antigen testing
- Confirmatory: Western blot
- Viral load using NASBA or RT-PCR
- Secondary testing (if needed): viral culture, lymph node biopsy, proviral DNA PCR, genotyping of viral DNA/RNA
- Other tests: CBC (shows anemia, thrombocytopenia, neutropenia); ESR may be elevated; polyclonal hypergammaglobulinemia.

MANAGEMENT:

Principles of antiretroviral (HAART) therapy:

- Antiretroviral therapy should be initiated in all patients regardless of CD4 counts with priority given to patients in WHO stage 3 or 4 or patients with CD counts ≤350 cells/µl.
- Priority should also be given to patients who have any of the following:
    - Pregnancy
    - AIDS-defining conditions
    - Acute opportunistic infections
    - Lower CD4 counts
    - HIV-associated nephropathy
    - Acute/ early infection
    - Hepatitis B or C coinfection
- Combination therapy should be given with at least three drugs from two different classes.
- Choosing a regime depends upon patient's prior treatment, virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interactions, side effects, drug resistance and patient's comorbids.
- Examples of regimens include:
    - Tenofovir + Emtricitabine + Efavirenz
    - Tenofovir + Emtricitabine + Darunavir/ Ritonavir
    - Tenofovir + Emtricitabine + Atazanavir/ Ritonavir
    - Tenofovir + Emtricitabine + Raltegravir
    - Tenofovir + Emtricitabine + Dolutegravir
    - Tenofovir + Emtricitabine + Elvitegravir + Cobicistat
    - Abacavir + Lamivudine + Dolutegravir

Table 3.8. CDC CATEGORY B HIV INFECTION: AIDS-RELATED ILLNESSES

INFECTIOUS	NON- INFECTIOUS
Oropharyngeal candidiasis	Cervical dysplasia/ cervical carcinoma in situ
Bacillary angiomatosis	Oral hairy leukoplakia
Persistent or resistant vulvovaginal candidiasis	Idiopathic thrombocytopenic purpura
Pelvic inflammatory disease	Constitutional symptoms e.g. fever or diarrhea lasting more than 1 month
Herpes zoster involving two or more episodes or one or more dermatomes	Peripheral neuropathy

Table 3.9. CDC CATEGORY C HIV INFECTION: AIDS DEFINING ILLNESSES

INFECTIOUS	NON-INFECTIOUS
Bronchial, tracheal, pulmonary or esophageal candidiasis	Invasive cervical cancer
Extrapulmonary or disseminated coccidiomycosis	Kaposi sarcoma
Extrapulmonary cryptococcosis	Burkitt lymphoma
Chronic intestinal cryptosporidiosis (>1 month)	Immunoblastic lymphoma
Cytomegalovirus disease (other than hepatic, splenic or nodal)	Primary lymphoma of brain
Cytomegalovirus infection (with vision loss)	Progressive multifocal leucoencephalopathy
Herpes simplex ulcers (>1 month duration), bronchitis, pneumonitis or esophagitis	HIV-related encephalopathy
Disseminated or extrapulmonary histoplasmosis	HIV wasting syndrome
Chronic intestinal isosporiasis (>1 month)	
Mycobacterial infections	
Atypical mycobacterial infections (M. avium complex and M. kansasii)	
Pneumocystis pneumonia	
Recurrent pneumonia	
Recurrent salmonella septicemia	
Toxoplasmosis of brain	

Classes of anti-retroviral drugs:

- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Fusion inhibitors
- CCR5 co-receptor antagonists (entry inhibitors)
- HIV integrase strand transfer inhibitors

Prophylaxis for opportunistic infections:

1. Pneumocystis jiroveci: Trimethoprim-sulfamethoxazole when CD4 count <200/µl (alternatives dapsone, atovaquone or nebulized pentamidine).
2. Toxoplasmosis: Trimethoprim-sulfamethoxazole when CD4 count <100/µl when not already receiving it.
3. Mycobacterium avium complex: azithromycin or clarithromycin when CD4 count <50/µl.
4. Mycobacterium tuberculosis: Isoniazid and pyridoxine to all PPD positive patients.
5. Cytomegalovirus infections: Oral ganciclovir CD4 count <50/µl.
6. Fungal infections: Oral fluconazole.

3.5.13. HERPES SIMPLEX VIRUS INFECTIONS (HSV)

"These are a group of infections caused by primary infection or reactivation of latent HSV."

QUICK FACTS: HSV	
Pathology:	**Virus infects and replicates locally → spreads retrogradely via neurons to dorsal root ganglia → becomes latent**
Presentation:	**Gingivostomatitis, pharyngotonsillitis, herpes labialis, herpes genitalis, whitlow, encephalitis, eczema herpeticum, disseminated herpes**
Diagnosis:	**Clinical diagnosis** **HSV culture, Tzank smear, PCR**
Treatment:	**Antivirals: acyclovir, famciclovir, valaciclovir**

VIRUS CHARACTERISTICS:

- Linear double-stranded DNA viruses.
- They are of two types:
    - Herpes simplex type 1 – usually associated with oral infection
    - Herpes simplex type 2 – usually associated with anogenital infection

TRANSMISSION:

- Direct or indirect contact with a patient with active herpes
- Contact with saliva or genital secretions

PATHOPHYSIOLOGY:

- Virus replicates at primary site of infection → carried retrogradely to dorsal root ganglia
- Virus becomes latent in the nerve cell ganglia proximal to site of infection → can get re-activated by various stimuli e.g. fever, trauma, etc.

PRESENTATION:

1. Herpes gingivostomatitis: Starts with tingling or itching inside mouth → fever and regional lymphadenopathy along with appearance of painful sores which lasts 10 – 14 days.
2. Herpes pharyngotonsillitis: fever, malaise, headache, sore-throat → vesicles rupture → grayish exudates on tonsils and posterior pharynx.
3. Herpes labialis (aka cold sores or fever blisters): It usually occurs as a recurrence of oral infection. It starts with a trigger e.g. certain foods, trauma, fever, etc. → tingling area in mouth → redness and swelling → blister formation (usually single) → breaks open → formation of sore → scab formation.
4. Herpes genitalis: Painful or itchy vesicles develop on or near external genitalia of males and females along with fever, headache, malaise and myalgias. It can lead to vaginitis, cervicitis in females and urethritis in both males and females. Proctitis occurs in patients who have anal sex.
5. Recurrence of herpes genitalis: painful or burning vesicles on genital areas. Sacral neuralgia may occur in some patients.
6. Herpes keratoconjunctivitis: small vesicles develop on cornea which rupture. Dendritic ulcers are characteristic. Deeper involvement of cornea can lead to blindness.
7. Herpetic whitlow: occurs when virus enters through a break in the skin of a finger → red, painful swollen finger-tips. It usually occurs in health-care workers and dentists whose fingers come in contact with secretions or lesions.
8. Eczema herpeticum: development of superimposed HSV infection in patients with atopic eczema.
9. Herpes encephalitis: it is a hemorrhagic encephalitis particularly involving frontal and temporal lobes. It presents with fever, headache, altered behavior and focal neurological findings.
10. Disseminated herpes: occurs in immunocompromised patients.
11. Neonatal herpes: HSV can be transmitted to neonate during pregnancy or birth → skin, mouth, eye involvement + CNS and visceral involvement.

INVESTIGATIONS:

- Clinical diagnosis
- HSV culture

- Tzank smear
- PCR
- Immunofluorescence

MANAGEMENT:
- Mild infection does not require treatment.
- Blisters or sores may be covered with hydrocolloid patch.
- Severe infection is treated antiviral agents: ACICLOVIR, VALACICLOVIR, FAMCICLOVIR.
- Topical antivirals may shorten duration of recurrences of ginigivostomatitis.
- In keratoconjunctivitis → topical or systemic antivirals
- For stromal keratitis or uveitis add steroids.
- Encephalitis is treated with intravenous ACICLOVIR.

3.5.14. VARICELLA-ZOSTER VIRUS INFECTION (VZV)

Aka human herpes virus type 3

"These are a group of infections caused by primary infection or reactivation of latent varicella-zoster virus."

QUICK FACTS: VARICELLA-ZOSTER VIRUS INFECTION	
Pathology:	**Virus infects lymphocytes → viremia → rash** **Latent infection in sensory ganglia → can reactivate later as shingles**
Presentation:	**Chicken pox: constitutional symptoms → itchy macules → vesicles → pustules → scabs +/- complications** **Herpes zoster (reactivation): dermatomal rash** **Other presentations: zoster multiplex, Ramsay Hunt syndrome, encephalomyelitis**
Diagnosis:	**Clinical diagnosis, Tzank smear, culture or PCR**
Treatment:	**Symptomatic** **? Antiviral therapy (decreases duration and severity)**

VIRAL CHARACTERISTICS:
- Linear double stranded DNA viruses
- Incubation period: 11 – 20 days

TRANSMISSION:
- Via aerosols from skin vesicles to the respiratory tract
- Via direct contact with vesicular fluid
- Trans-placental passage

PATHOPHYSIOLOGY:
- Primary infection: infects lymphocytes → viremia → rash
- After primary infection virus establishes latency in the sensory ganglia from where it can get reactivated → leads to herpes zoster.
- Infectivity period: 4 days before rash appears until last vesicles crust.

PRESENTATION:
1. Chicken pox: After incubation period of 10 – 21 days there is appearance of fever, tiredness, anorexia, headache → itchy rash on day 1 or 2 in the form of macules which progress to vesicles, pustules and subsequently form scabs (in about one week) which shed. Rash begins from face, chest and back and later spreads to limbs (centrifugal). Rash is pleomorphic (multiple stages of rash present at a time). Each crop of rash comes with fever and occurs every 2 – 4 days. Complications include varicella pneumonia, meningoencephalitis, cerebellar ataxia and bacterial infections.
2. Herpes zoster (or shingles): pain and paresthesias in a sensory dermatomal pattern (usually thoracic) occasionally with flu-like symptoms, helplessness and depression → erythematous macules and

papules → grouped herpetiform vesicles on an erythematous base → crusting. Patients may also develop pain and hypoesthesia in the same area ± regional motor weakness. Regional lymphadenopathy may also occur.
3. Zoster multiplex: shingles in multiple dermatomes which can occasionally be bilateral.
4. Postherpetic neuralgia: neuropathic pain after resolution of herpes zoster.
5. Herpes zoster oticus (Ramsay Hunt syndrome): Aka geniculate neuralgia/ nervus intermedius neuralgia. It is an acute peripheral facial neuropathy associated with herpes zoster of external ear and/ or oropharyngeal mucosa.
6. Zoster sine herpete: Herpes zoster or Ramsay Hunt syndrome in the absence of skin rashes.
7. Herpes zoster ophthalmicus: caused by reactivation of VZV in the ophthalmic division of trigeminal nerve → conjunctivitis or corneal ulcers → can cause blindness.
8. Encephalomyelitis, myelitis, pneumonia, hepatitis
9. Disseminated herpes zoster: usually occurs in immune-compromised patients
10. Congenital varicella syndrome: occurs when there is maternal infection in first two trimesters of pregnancy. Features include atypical scarring of skin, IUGR, cataracts, cerebral atrophy and limb atrophy.

INVESTIGATIONS:

- Diagnosis is clinical. If in doubt perform Tzank smear or culture of vesicle fluid or DNA analysis.

MANAGEMENT:

- Chickenpox:
  - Symptomatic treatment. Emollients.
  - Antivirals within 24 hours of rash: ACYCLOVIR, VALACYCLOVIR, PENCICLOVIR or FAMCICLOVIR.
  - Antiviral therapy decreases duration of rash and incidence of post-herpetic neuralgia especially when initiated within two days of onset of rash.
  - Lysimachia mauritiana extract promising.
- Herpes zoster:
  - Herpes zoster is usually self-limited. In uncomplicated cases treatment is conservative.
  - Neuropathic pain: amitriptyline, gabapentin, analgesics, topical capsaicin.
- Varicella zoster immune globulin (VZIG) can be given to individuals at high risk of acquiring chicken pox. It can be given up to 10 days after exposure (ideally within 7 days).
- VZV vaccine: live attenuated vaccine

3.5.15. EPSTEIN-BARR VIRUS INFECTION (EBV)

Aka human herpes virus type 3

"It is an infection of reticulo-endothelial cells caused by infection with Epstein-Barr virus."

QUICK FACTS: EBV	
Pathology:	**EBV infects B-cells in pharynx → spreads to reticuloendothelial cells**
Presentation:	**Infectious mononucleosis: fatigue, malaise, fever, sore-throat, arthralgias, myalgias, hepatosplenomegaly, tonsillar enlargement** **Malignancies: nasopharyngeal carcinoma, Hodgkin's lymphoma, Burkitt's lymphoma, DLBCL, post-transplant B-cell lymphoma, hairy leukoplakia in HIV**
Diagnosis:	**Non-specific antibodies: monospot test, Paul-Bunell test** **Specific antibodies: IgM/ IgG of VCA and EBNA**
Treatment:	**Symptomatic treatment**

VIRAL CHARACTERISTICS:

- Linear double stranded DNA viruses

TRANSMISSION:

- Via mucosal contact with body fluids especially saliva e.g. kissing (aka kissing disease)
- Via sexual contact
- Via blood transfusions
- Via organ transplantation

- Via sharing of objects which come in contact with body secretions like toothbrush.

PATHOPHYSIOLOGY:

- EBV infects B cells of oropharynx → circulating B cells spread infection to reticulo-endothelial system → B- and T- cell response
- If ineffective T-cell response → B-cell hyperproliferation → B-cell lymphomas

PRESENTATION:

1. Infectious mononucleosis (aka glandular fever): Mostly asymptomatic. Symptoms include fatigue, prolonged malaise, sore-throat, low-grade fever, nausea, anorexia and cough. Rarely arthralgias and myalgias. Signs include cervical lymphadenopathy, pharyngitis (usually exudative), tonsillar enlargement, rash (maculopapular), peri-orbital edema, jaundice, splenomegaly, relative bradycardia, uvular edema, palatal petechiae in posterior oropharynx. Rarely splenic rupture may occur. Rash may appear or worsen after using penicillins e.g. amoxicillin.
2. Complications: splenic rupture, cranial nerve palsies, pharyngeal edema, thrombocytopenia
3. Malignant associations:
    a. Nasopharyngeal carcinoma
    b. Hodgkin's lymphoma
    c. Burkitt's lymphoma
    d. Diffuse large B cell lymphoma
    e. B-cell lymphomas in post-transplantation patients
    f. HIV-related hairy leukoplakia
    g. Leiomyomas and leiomyosarcomas in immunocompromised patients
    h. X-linked lympho-proliferative disease (Duncan's syndrome)

INVESTIGATIONS:

- Tests for non-specific antibodies:
    - Monospot test: agglutination of horse RBCs by heterophile antibodies. If suspected start with Monospot test. If negative then repeat every week for 6 weeks.
    - Paul-Bunell test: agglutination of sheep RBCs by heterophile antibodies.
- Tests for specific antibodies:
    - IgM VCA or IgG VCA antibodies (viral capsid antigens)
    - IgM EBNA or IgG EBNA antibodies (viral nuclear antigens)
- CBC: leukocytosis with lymphocyte predominance; atypical lymphocytosis (usually >10%); thrombocytopenia
- ESR: raised
- LFT's: elevated transaminases

MANAGEMENT:

- There is no specific treatment. Do symptomatic treatment.
- Avoid contact sports (to avoid splenic rupture).
- Steroids in case of pharyngeal edema, neurologic involvement, hemolysis and thrombocytopenia.

⇨ ***Triad of infectious mononucleosis = fever + lymphadenopathy + pharyngitis***

⇨ ***Mononucleosis like syndromes: HIV, HHV-6, toxoplasmosis, CMV, rubella. Also Phenytoin and Dapsone.***

3.5.16. CYTOMEGALOVIRUS INFECTION (CMV)

Aka human herpes virus type 4

QUICK FACTS: CMV	
Pathology:	**CMV infection → becomes latent in myeloid cells → in immunocompromised may affect retina, lungs, brain, kidneys, etc.**
Presentation:	**Asymptomatic** **Mononucleosis syndrome** **Immunocompromised:, transaminitis, retinitis, encephalitis, pneumonia, hepatitis, colitis, cytopenias** **Congenital CMV: jaundice, splenomegaly, thrombocytopenia, IUGR, microcephaly, retinitis**
Diagnosis:	**Atypical lymphocytes on peripheral film** **Negative heterophile antibody tests** **IgM, IgG, CMV pp65 antigen in WBCs, PCR** **Biopsy: owl's eye appearance** **Human fibroblast culture**
Treatment:	**Immunocompetent: no treatment** **Immunocompromised: valganciclovir, ganciclovir, foscarnet, cidofovir, maribavir**

VIRAL CHARACTERISTICS:

- Double-stranded DNA virus of herpesviridae

TRANSMISSION:

- Person to person through body fluids
- Through organ transplantation
- Trans-placental

PATHOPHYSIOLOGY:

- Primary infection → becomes latent in myeloid cells

PRESENTATION:

In asymptomatic patients:

1. Primary infection is asymptomatic (usually)
2. Flu-like illness (sometimes)
3. Fever of unknown origin
4. Organ involvement like e.g. transaminitis, encephalitis, colitis, cytopenias, retinitis
5. Mononucleosis syndrome (usually occurs in immnocompromised patients):
6. Congenital CMV disease: jaundice, splenomegaly, thrombocytopenia, intrauterine growth retardation, microcephaly, retinitis.

In immunocompromised patients:

1. It presents as bone marrow suppression, pneumonia, hepatitis, myocarditis, encephalitis, myelitis, gastritis, colitis, nephritis, pancreatitis, uveitis, retinitis and neuropathy.
2. CMV retinitis: occurs in patients with HIV/ AIDS, post-transplant patients and immunocompromised patients. It is a viral necrotizing retinitis which starts from mid-periphery and spreads in a brushfire pattern. It can lead to blindness.

Rare presentations include:

1. Guillain-e-Barré syndrome
2. Meningoencephalitis
3. Pericarditis
4. Myocarditis
5. Thrombocytopenia
6. Hemolytic anemia

INVESTIGATIONS:

- CBC: atypical lymphocytes
- Negative heterophile antibody tests

- Elevated IgM or four-fold rise in IgG titer.
- Detection of CMV pp65 antigen in leucocytes.
- PCR in blood and tissues
- Intracellular inclusions surrounded by clear halo (owl's eye pattern) in biopsied tissue.
- Human fibroblast culture.

MANAGEMENT:
- Immunocompetent persons do not require any treatment.
- For solid organ transplantation: VALGANCICLOVIR (risk of neutropenia)
- For other manifestations: GANCICLOVIR (risk of neutropenia)
- Second-line treatments: FOSCARNET, CIDOFOVIR, MARIBAVIR
- HAART therapy in those with AIDS

⇨ ***CMV retinitis is the most common presentation of CMV in HIV patients.***

3.5.17. KAPOSI'S SARCOMA ASSOCIATED HERPES VIRUS

Aka human herpes virus type 8

QUICK FACTS: KS ASSOCIATED HERPES VIRUS	
Pathology:	**After infection becomes latent in lymphocytes, monocytes and endothelial cells. Kaposi's sarcoma**
Presentation:	**Primary effusion lymphoma Castleman's disease (some variants)**
Diagnosis:	**HIV workup HHV-8 DNA PCR Serology**
Treatment:	**HAART Localized disease: Surgery, radiation Generalized disease: interferon, chemotherapy**

VIRUS CHARACTERISTICS:
- Double-stranded DNA virus

TRANSMISSION:
- ? sexual transmission
- ? saliva

PATHOPHYSIOLOGY:
- It is an oncovirus. It becomes latent in lymphocytes, monocytes and endothelial cells.

PRESENTATION:
- Kaposi sarcoma in AIDS: It is a spindle-cell tumor. It presents as palpable non-pruritic discrete or confluent macules, papules, nodules or plaques with brown, pink, red or violaceous color. Mucosal membranes may be involved.
- Primary effusion lymphoma (body cavity based lymphoma)
- Some variants of Castleman's disease

INVESTIGATIONS:
- HIV workup
- HHV-8 DNA PCR
- Serological tests
- Biopsy

MANAGEMENT:
- HAART therapy for AIDS

- Localized Kaposi sarcoma: surgical removal or radiation therapy
- Immunomodulators: Interferon alfa
- Chemotherapeutic agents.

3.5.18. PARVOVIRUS INFECTION

QUICK FACTS: PARVOVIRUS	
Pathology:	**Virus infects erythroid precursor cells → arrests erythropoiesis**
Presentation:	**Asymptomatic** **Fever, slapped-cheek rash on face, macular lacy reticular rash** **Arthralgias** **Aplastic crises**
Diagnosis:	**IgM, IgG** **DNA PCR**
Treatment:	**Supportive care** **IVIG (immunocompromised)**

VIRUS CHARACTERISTICS:
- Non-enveloped single strand DNA virus of Parvoviridae

TRANSMISSION:
- Humans are the only natural hosts.
- It is transmitted from person-to-person by respiratory secretions and by fomites.
- Virus replicates in erythroid precursor cells which bear blood group P antigen and lead to arrest of erythropoiesis.

SYMPTOMS AND SIGNS:
- Mostly asymptomatic.
- **Erythema infectiosum:** Low-grade fever with **facial slapped-cheek rash** followed by **macular lacy reticular rash**.
- Arthralgias
- Aplastic crisis
- Pure red cell aplasia
- Hydrops fetalis

INVESTIGATIONS:
- Parvovirus B19 specific IgM , IgG
- DNA detection by PCR

TREATMENT:
- Supportive care
- Blood product transfusion.
- IV IMMUNOGLOBULINS in immunosuppressed patients.

3.6. BACTERIAL INFECTIONS

Table 3.10. CLASSIFICATION OF MEDICALLY IMPORTANT BACTERIA

Lacking cell wall							Mycoplasma Ureaplasma
Rigid cell wall	Simple unicellular	Obligate intracellular					Chlamydia Coxiella Rickettsia Ehrlichia
		Free living	Gram positive	Cocci			Streptococcus Staphylococcus Enterococcus Peptostreptococcus
				Bacilli			Bacillus Clostridium Corynebacterium Erysipelothrix Lactobacillus Listeria Propionobacterium
			Gram negative	Cocci			Moraxella Neisseria
				Bacilli	Lactose fermenting	Oxidase positive	Pasturella Vibrio Aeromonas
						Oxidase negative	Escherichia Salmonella Shigella Enterobacter Citrobacter Serratia Yersinia Proteus Providencia Morganella
					Non-lactose fermenting	Oxidase positive	Pseudomonas
						Oxidase negative	Stenotrophomonas Acinetobacter
						Strict anerobe	Bacteroides Fusobacterium Prevotella Porphyromonas
					Other requirements		Haemophilus Campylobacter Legionella Bordetella Brucella Francisella Stenotrophomonas Acinetobacter Bartonella Helicobacter
	Filamentous						Actinomyces Mycobacteria Nocardia
Spirochaetes							Treponema Leptospira Borellia

3.6.1. MYCOPLASMA INFECTIONS

"It is a group of infections caused by Mycoplasma pneumoniae."

QUICK FACTS: MYCOPLASMA INFECTIONS	
Pathology:	**Mycoplasma infects epithelial cells → mononuclear inflammation**
Presentation:	**Tracheo-bronchitis or bronchiolitis** **Pharyngitis** **Pneumonia**
Diagnosis:	**Cold agglutinin titer** **ELISA**
Treatment:	**Macrolides** **Tetracyclins, clindamycin, fluoroquinolones**

BACTERIAL CHARACTERISTICS:

- Wall-less bacteria

PATHOPHYSIOLOGY:

- Pathogen attaches to respiratory epithelial cells → local inflammation with mononuclear cells

PRESENTATION:

1. Tracheo-bronchitis or bronchiolitis
2. Pharyngitis: presents as sore-throat
3. Pneumonia (aka walking pneumonia/ primary atypical pneumoniae): presents as sore-throat, fever, dry cough, body aches, hoarse voice and dyspnea. Extra-pulmonary manifestations may predominate. These include CNS manifestations (encephalitis, meningitis, infarcts, polyradiculitis), skin manifestations (SJS, erythema multiforme), hematological manifestations (autoimmune hemolytic anemia due to cold agglutinins, autoimmune thrombocytopenia, DIC), skeletal manifestations (arthralgias, myalgias).

INVESTIGATIONS:

- CBC: occasional leukocytosis
- ESR: sometimes raised
- Sputum examination: negative Gram stain
- Cold agglutinin titre
- Serological tests: ELISA
- Culture on special media
- PCR for M. pneumoniae
- CXR: diffuse or interstitial infiltrates particularly in lower lobes and sometimes pleural effusion

TREATMENT:

- Drug of choice: Macrolides e.g. erythromycin, azithromycin, clarithromycin
- Other options: tetracyclins, clindamycin, fluoroquinolones

⇨ ***Mycoplasma pneumonia is the most common cause of atypical pneumonia.***

⇨ ***Mycoplasma has been implicated in etiopathogenesis of atherosclerosis and asthma.***

⇨ ***Genital mycoplasma infections and ureaplasma infections include urethritis, cervicitis, endometritis and pelvic inflammatory disease.***

3.6.2. CHLAMYDIAL INFECTIONS

QUICK FACTS: CHLAMYDIAL INFECTIONS	
Pathology:	**Infectious elementary body → infects cells particularly squamo-columnar cells → form reticulate body → undergoes binary fission → forms elementary body → cells rupture → re-infect new cells**
Presentation:	**Genitourinary infections (C. trachomatis) Perihepatitis (Fitzhugh-Curtis syndrome) Lymphogranuloma venereum (C. trachomatis) Eye infections Lung infections**
Diagnosis:	**Chlamydial cultures, NAAT**
Treatment:	**Azithromycin and other macrolides, doxycycline, fluoroquinolones**

BACTERIAL CHARACTERISTICS:

- Gram-negative intra-cellular organisms

Include three main organisms

- Chlamydia psittaci
- Chlamydia trachomatis
- Chlamydia pneumonia

PATHOPHYSIOLOGY:

- Incubation period: 7 – 14 days
- Elementary bodies penetrate cells (mainly squamo-columnar cells) → changes to reticulate bodies (seen as intracellular inclusions) → re-organize into elementary bodies → rupture cell → re-infection of new cells.

PRESENTATIONS:

- Chlamydial genitourinary infections in females: caused by C. trachomatis and include following:
  - Cervicitis, salpingitis and endometritis
  - Pelvic inflammatory disease: also associated with infertility
  - Dysuria-Pyuria syndrome or urethritis: frequency, dysuria, lower abdominal pain, pyuria
  - Perihepatitis (Fitzhugh-Curtis syndrome): inflammation of liver capsule and surrounding peritoneum
  - Chlamydia infection during pregnancy may cause premature rupture of membranes or low-birth-weight infants. It is also associated with miscarriages.
- Chlamydial genitourinary infections in males may cause urethritis, epididymitis, prostatitis and in homosexuals it may cause proctatitis.
- Lymphogranuloma venereum: It is caused by C. trachomatis. It is acquired by intercourse or contact with exudate from lesions. Vesicular or ulcerative lesions develop. 1 – 4 weeks after these localized inguinal lymphadenopathy (buboes) occurs.
- Chlamydial eye infections:
  - C. trachomatis : conjunctivitis and trachoma in newborns of mothers with infected genital tracts
- Chlamydial lung infections :
  - C. trachomatis: newborns of mothers with infected genital tracts may develop pneumonia after birth
  - C. pneumonia: causes pharyngitis, bronchitis and pneumonia
  - C. psittaci: causes psittacosis/ ornithosis (fever, chills, malaise, dry cough, dyspnea and other features). It spreads by inhaling respiratory droplets or aerosols of dried excreta of birds.
- There is increased risk of developing cervical cancer and HIV infection.

INVESTIGATIONS:

- Urine D/R may show leukocytes however traditional cultures are negative (sterile pyuria)
- Chlamydial cultures of urethral, vaginal, nasopharyngeal and conjunctival swabs or urine
- Nucleic acid amplification tests (NAAT)
- Antigen detection
- Genetic probes
- Rapid tests e.g. enzyme immunoassays

TREATMENT:

- Antibiotics include azithromycin and doxycycline as first line therapy. Others include erythromycin, levofloxacin, ofloxacin and sulfisoxazole. Mild infections are treated with a single dose of AZITHROMYCIN 1g or a 7 day course of DOXYCYCLINE or LEVOFLOXACIN.
- Complicated cases/ pelvic inflammatory disease need treatment with a second or third generation cephalosporin with a 14 days course of doxycycline with or without metronidazole OR clindamycin with gentamicin OR ampicillin-sulbactam with doxycycline.
- Lymphogranuloma venereum is treated with 21 days of DOXYCYCLINE or ERYTHROMYCIN or AZITHROMYCIN.
- Conjunctivitis and pneumonia are treated for 14 days.
- During pregnancy: azithromycin, amoxicillin or erythromycin.
- Both partners and mother of infected child must be treated simultaneously.
- Sexually active people should take precautions.

⇨ ***Genitourinary chlamydia infection is associated with Reiter's syndrome.***

⇨ ***Chlamydia pneumonia is the second most common cause of atypical pneumonia (first is Mycoplasma pneumonia).***

3.6.3. RICKETTSIAL AND RELATED INFECTIONS

"These are a group of infections caused by obligate intracellular gram-negative bacteria."

PREVENTION:

- No vaccine available.
- Minimize exposure to vectors during travel.
- Use insect or tick repellants.
- Do self-examination after travel through endemic areas.

3.6.3.1. EHRLICHIOSIS

- **Causative organism:** Ehrlichia chaffeensis
- **Acquired by:** Amblyomma tick bite
- **Features:** Infects monocytes. Asymptomatic or flu-like illness.
- **Investigations:** Leukopenia, thrombocytopenia, cytoplasmic inclusions in monocytes (morulae), elevated transaminases. PCR is diagnostic.
- **Treatment:** Doxycycline

3.6.3.2. ANAPLASMOSIS

- **Causative organism:** Anaplasma phagocytophilum
- **Acquired by:** Ixodid tick bite
- **Features:** Infects neutrophils. Asymptomatic or flu-like illness.
- **Investigations:** Leukopenia, thrombocytopenia, cytoplasmic inclusions in neutrophils, elevated transaminases. PCR is diagnostic.
- **Treatment:** Doxycycline

3.6.3.3. SCRUB TYPHUS

- **Causative organism:**Orientia tsutsugamushi
- **Acquired by:** Trombiculid mite bite.
- **Features:** An eschar evolves at the bite site. Other features include high-grade fever with chills and rigors, tender regional lymphadenopathy, headache, conjunctival hyperemia, pneumonitis and anorexia.
- **Investigations:** Early lymphopenia, late lymphocytosis. Serological tests are diagnostic.
- **Treatment:** Tetracyclines, macrolides, fluoro-quinolones.

3.6.3.4. ROCKY MOUNTAIN SPOTTED FEVER

- **Causative organism:**Rickettsia rickettsia
- **Acquired by:** Dog tick bite
- **Features:** Fever, headache, maculopapular rash (involving palms and soles), confusion, abdominal pain, diarrhea and myalgias occur.
- **Investigations:** Initially leukopenia then mild leukocytosis, thrombocytopenia, mild transaminitis. Serological tests are diagnostic.
- **Treatment:** Doxycycline

3.6.3.5. EPIDEMIC/ SYLVATIC TYPHUS

- **Causative organism:**Rickettsia prowazekii
- **Acquired by:**Inoculation of fecal matter of human body louse

- **Features:**Abrupt fever, headache, maculopapular/ petechial rash, rigors, splenomegaly and CNS symptoms.
- Disease may recrudesce years after attack in a milder form (Brill-zinsser disease).
- **Investigations:**Biopsy of rash, serological tests, PCR
- **Treatment:**Doxycycline, chloramphenicol

3.6.3.6. ENDEMIC/ MURINE TYPHUS

- **Causative organism:**Rickettsia typhi, Rickettsia felis
- **Acquired by:**Rat and cat fleas
- **Features:**Fever, headache, shaking chills, rash
- **Investigations:**Biopsy of rash, serological tests, PCR
- **Treatment:**Doxycycline

3.6.3.7. Q FEVER

- It is now classified separate from rickettsial diseases.
- **Causative organism:**Coxiella burneti
- **Acquired by:** Inhalation of aerosols from contaminated soil or animal waste (cattle, sheep, goats); tick-bites, ingestion of unpasteurized milk or dairy products.
- **Features:**
- Acute: Influenza-like illness, hepatitis, pneumonia
- Chronic: Culture-negative endocarditis
- **Investigations:** PCR, serological tests
- **Treatment:** Doxycycline or trimethoprim-sulfamethoxzole

Table 3.11. LIST OF RICKETTSIAL DISEASES

Group of organisms	Organisms	Disease
Anaplasma	Anaplasma phagocytophilum	Human anaplasmosis
Ehrlichia	Ehrlichia chaffeensis	Human ehrlichiosis
Neoehrlichia	Neoehrlichia mikurensis	Human neoehrlichiosis
Neorickettsia	Neorickettsia sennetsu	Sennetsu fever
Orientia	Orientia tsutsugamushi	Scrub typhus
Rickettsia (spotted fevers)	Rickettsia rickettsia	Rocky mountain spotted fever
	Rickettsia japonica	Japanese spotted fever
	Rickettsia akari	Rickettsialpox
	Rickettsia conorii	Mediterranean spotted fever
Rickettsia (typhus fevers)	Rickettsia prowazekii	Endemic/ sylvatic typhus
	Rickettsia typhi	Murine typhus
Coxiella	Coxiella burnetii	Q fever

Table 3.12. LIST OF STREPTOCOCCAL INFECTIONS		
Group of streptococci	**Example**	**Diseases**
Group A ß-hemolytic streptococci (GAS)	S. pyogenes	Pharyngitis Impetigo Cellulitis Necrotizing fasciitis Arthritis Sepsis Pneumonia Empyema Endocarditis Scarlet fever Streptococcal toxic shock syndrome Acute rheumatic fever Post-streptococcal glomerulonephritis
Group B ß-hemolytic streptococci	S. agalactiae	Neonatal sepsis Neonatal meningitis
Group D streptococci (enterococcal)	E. faecalis E. faecium	Urinary tract infections Endocarditis Biliary tract infections Wound infections
Group D streptococci (non-enterococcal)	S. bovis	Endocarditis
S. pneumoniae		Pneumonia Otitis media Meningitis
Viridans streptococci		Endocarditis

3.6.4. STREPTOCOCCAL INFECTIONS

BACTERIAL CHARACTERISTICS:

- Gram-positive, catalase negative cocci in chains

SPECTRUM OF INFECTIONS:

- Different species of streptococci cause a wide variety of infections:

⇨ ***Streptococcus pneumonia is most common cause of community-acquired pneumonia, sinusitis, otitis media, mastoiditis, meningitis and sepsis in asplenic patients.***

⇨ ***S. pyogenes is the most common cause of bacterial pharyngitis.***

3.6.4.1. PHARYNGITIS

PRESENTATION:

- Fever, sore-throat, odynophagia, tender cervical lymphadenopathy, malaise and nausea
- Pharynx, tonsils and soft palate are congested and may show purulent exudate

INVESTIGATIONS:

- Centor criteria (see table 3.13.)
- General investigations may show neutrophilia.
- Culture on blood agar plate

COMPLICATIONS:

- Suppurative complications: sinusitis, otitis media, mastoiditis, peritonsillar abscess, suppurative cervical lymphadenitis.
- Non-suppurative complications: rheumatic fever, glomerulonephritis

TREATMENT:

- Antibiotic therapy should be given after confirmation of diagnosis.
- Antibiotics include penicillins, cephalosporins and macrolides.

Table 3.13. CENTOR CRITERIA FOR DIAGNOSIS OF STREPTOCOCCAL PHARYNGITIS
1. Pharyngo-tonsillar exudate 2. Tender anterior cervical lymphadenopathy 3. Fever >100.5°F 4. Absence of cough
Absence of 3 – 4 criteria rules out streptococcal sore-throat. Presence of 3 out of 4 criteria likely streptococcal sore-throat.

3.6.4.2. SCARLET FEVER

Aka Second disease

"It is an exudative pharyngitis along with fever and diffusely red erythematous rash."

PATHOPHYSIOLOGY:

- Pharyngeal infection with group A ß-hemolytic streptococci → circulating toxin (erythrogenic toxin or pyrogenic erythrotoxin) → rash

PRESENTATION:

- Fever
- Exudative pharyngitis
- Diffuse red erythematous rash which is dense in region of axilla and groin
- Flushed face
- Circumoral pallor
- Strawberry tongue (enlarged red papillae on tongue)

TREATMENT:

- Give early antibiotics to prevent complications. These include penicilins, cephalosporins, clindamycin or erythromycin.

3.6.4.3. PNEUMOCOCCAL INFECTIONS

"These are different diseases caused by Streptococcus pneumonia."

QUICK FACTS: PNEUMOCOCCAL INFECTIONS	
Pathology:	**Streptococci lodge in nasopharynx → invade to respiratory and other neighboring structures → hematogenous spread to other organs**
Presentation:	**Upper respiratory tract infections, otitis media, pharyngitis, sinusitis, conjunctivitis, bronchitis, pneumonia** **Meningitis** **Sepsis**
Diagnosis:	**Cultures**
Treatment:	**Beta-lactam antibiotics, macrolides, fluoroquinolones**

CAUSATIVE ORGANISM:

- Streptococcus pneumonia (gram-positive, catalase negative organisms)

PATHOPHYSIOLOGY:

- S. pneumonia are acquired by inhalation and lodge in nasopharynx → invade directly to other structures causing conjunctivitis, otitis media, sinusitis, bronchitis, pneumonia.
- Hematogenous spread may lead to meningitis, bacteremia, septic arthritis, osteomyelitis, myositis, peri-orbital cellulitis, abscess, endocarditis.
- Different presentations can occur together.

RISK FACTORS:

- Children (<5 years), elderly (>55 years); immunocompromised patients

PRESENTATION:

- Pneumococcal pneumonia:
  - Presents as fever, chills, cough, sputum (usually rust-colored), dyspnea and pleuritic chest pain.
  - Chest examination usually reveals findings of lobar consolidation.
  - It may complicate to parapneumonic effusion or empyema.
- Pneumococcal meningitis:
  - Presents as fever, headache, meningismus, photophobia, confusion and altered level of consciousness.
  - Signs of meningeal irritation are usually present.
  - Cranial nerve palsies may develop.
- Acute exacerbation of chronic bronchitis:
  - S. pneumonia is one of the most important cause of acute exacerbations of chronic bronchitis.
- Bacteremia/ sepsis:
  - Presents with symptoms and signs of sepsis.
- Otitis media:
  - Presents as ear-pain, red swollen ear-drum and sometimes fever.

INVESTIGATIONS:

- General investigations:
  - Complete blood picture
  - ESR and CRP
- Pneumonia:
  - Chest x-ray may reveal lobar consolidation, air-bronchogram, pleural effusion or empyema.
  - Gram stain and culture of sputum is diagnostic. Blood cultures may also be positive.
- Meningitis:
  - CSF examination shows: Elevated opening pressures; neutrophilic pleocytosis (WBCs >1000/µL, >60% neutrophils), hypoglycorrhacia (CSF glucose <40 mg/dL or <50% of serum glucose), raised CSF proteins (usually >150 mg/dL), gram positive organisms (in 80 – 90% of cases) and positive cultures.
  - Blood cultures may also be positive.
- Bacteremia/ sepsis:
  - Blood cultures are usually positive.
- Otitis media:
  - Culture

TREATMENT:

- For pneumonia:
  - Outpatients may be treated with macrolides or beta lactam antibiotics.
  - Inpatients may be treated with beta-lactam antibiotic plus macrolide or a fluoroquinolone.
  - Other supportive measures like intravenous hydration, anti-pyretics, oxygen, etc.
- For meningitis start antibiotics as soon as suspected
  - Empiric treatment with CEFTRIAXONE 2 g IV twice daily, VANCOMYCIN 15 mg/kg twice daily
  - Once organism is isolated then specific therapy can be started.
  - DEXAMETHASONE 0.15 mg/kg every 6 hours for four days. First dose should be given just before or along with the first dose of antibiotic.
- For otitis media and sinusitis:
  - Amoxicillin, amoxicillin-clavulanate, second or third generation cephalosporins. Fluoroquinolones may be used.

PREVENTION:

- Pneumococcal conjugate vaccine protects against 13 serotypes.
- Pneumococcal polysaccharide vaccine protects against 23 serotypes.

- Vaccination is recommended for all adults ≥65 years of age and for adults <65 years of age who have predisposing medical conditions (e.g. smoking, asthma, COPD, splenectomy).

3.6.4.4. OTHER STREPTOCOCCAL INFECTIONS

- Impetigo: See section in dermatology
- Erysipelas: See section in dermatology
- Cellulitis: See section in dermatology
- Arthritis:
    - It may occur in association with cellulitis.
    - It is treated with intravenous antibiotics, percutaneous needle aspirations or surgical drainage.
- Pneumonia:
    - May complicate into empyema.
    - Treated with high dose penicillin and chest tube drainage.
- Endocarditis: See section in cardiology
- Necrotizing fasciitis:
    - It is a rapidly spreading infection of the fascia of deep muscle.
    - Surgical debridement is necessary along with antibiotics.
- Gangrenous myositis
- Streptococcal toxic shock syndrome:
    - Erthrotoxin acts as a super-antigen and causes massive release of cytokines.
    - It is characterized by fever, rash, hypotension and multi-organ failure (≥3 organ systems) and desquamation of palms and soles.
    - Early recognition, supportive measures and early institution of antibiotics is necessary for survival. Antibiotics include penicillin G and/or clindamycin. Newer drugs include ORITAVANCIN, DALBAVANCIN and TEDIZOLID.

⇨ ***Viridans streptococci are the most frequent cause of native valve endocarditis.***

⇨ ***Streptococcus bovis typically causes endocarditis in patients with colorectal carcinoma or cirrhosis of liver.***

3.6.5. STAPHYLOCOCCAL INFECTIONS

Table 3.14. STAPHYLOCOCCAL INFECTIONS		
Staphylococcal group	**Staphylococcal type**	**Infections**
Coagulase-positive staphylococci	Staphylococcus aureus	Skin and soft tissue infections: Impetigo, furuncles, carbuncles, paronychia, cellulitis, folliculitis, hydradenitis suppurativa, abscesses Surgical wound infections Blepharitis Mastitis Sepsis and metastatic abscesses Osteomyelitis Septic arthritis Endocarditis (native and prosthetic valves) Pneumonia (especially in post-op patients and after viral infections e.g. influenza) Toxin-mediated diseases: food poisoning, toxic shock syndrome, scalded skin syndrome
Coagulase-negative staphylococci	Staphylococcus epidermidis	Native valve endocarditis (especially in intravenous drug users) Infections of iv catheters and prosthetic implants e.g. endocarditis, vascular grafts, prosthetic joints (septic arthritis and osteomyelitis)
	Staphylococcus saprophyticus	Urinary tract infections in patients with recent sex and in those with indwelling catheters

3.6.5.1. STAPHYLOCOCCUS AUREUS INFECTIONS

QUICK FACTS: STAPHYLOCOCCUS AUREUS INFECTIONS	
Pathology:	**Bacteria → replicate and invade → form infections or abscesses** **May produce toxins**
Presentation:	**Skin and soft tissue infections: impetigo, furuncles, carbuncles, abscesses, mastitis, wound infections, pyomyositis, septic bursitis, endocarditis, osteomyelitis, epidural abscess, septic arthritis, pneumonia, sepsis, purpura fulminans, toxic shock syndrome, food poisoning, scalded skin syndrome**
Diagnosis:	**Bacterial cultures**
Treatment:	**Uncomplicated infections: penicillinase resistant penicillins and cephalosporins e.g. dicloxacillin, cephalexin. Infections with MRSA require clindamycin, doxycycline, minocycline or trimethoprim-sulfamethoxazole** **Complicated infections: intravenous nafcillin, oxacillin, vancomycin, linezolid, daptomycin, tigecycline, telavancin or ceftaroline** **Drainage of abscesses**

PATHOGENESIS:

Organisms are acquired by direct contact e.g. iv catheters, contaminated implants, long-term tampon use, etc. They may cause disease by any two of the following:

- Replicate and invade locally → infection and abscesses → may metastasize via blood to other organs.
- Produce toxins some of which act as super-antigense.g toxic shock syndrome

PRESENTATION:

- Skin and soft tissue infections:
  - Impetigo: see section in dermatology
  - Furuncle:see section in dermatology
  - Carbuncle:see section in dermatology
  - Abscesses:see section in dermatology
  - Mastitis:

        - Usually occurs in lactating women.
        - Can lead to abscess formation.
    - Wound infections
    - Pyomyositis
        - It usually occurs in immunocompromised patients e.g. HIV.
        - It presents with fever, swelling and pain overlying involved muscle.
    - Septic bursitis
- Endocarditis: see section in cardiology
- Osteomyelitis: see section in rheumatology
- Epidural abscess:
    - It usually occurs as a complication of vertebral osteomyelitis.
    - It presents as fever, spinal pain, radicular pain and neurological deficits.
- Septic arthritis
- Pneumonia
    - It usually occurs in children.
    - In adults it can occur as CAP after viral infections like influenza and as HAP or VAP.
    - CAP patients usually present as fever, bloody sputum, mid-lung field pneumatocoeles and multiple patchy pulmonary infiltrates.
    - Nosocomial infections present as fever, increased respiratory secretions, new widespread patchy infiltrates and respiratory distress.
    - Methicillin-resistant staphylococcus aureus (MRSA) is a significant nosocomial threat with high mortality and spread. Increasing numbers of community-acquired MRSA (CA-MRSA) are being detected.
- Bacteremia/ sepsis:
    - S. aureus survive in neutrophils and can readily spread to multiple sites by hematogenous route.
    - It can lead to metastatic deposits in bones, joints, kidneys and lungs.
- Purpura fulminans: intravascular thrombosis and hemorrhagic infarction of skin. It leads to DIC.
- Toxic shock syndrome:
    - It is caused by toxins which act as superantigens. It is also caused by streptococci.
    - The toxins are produced from any focus of infection e.g. abscess, wound infection, long-standing tampons, etc.
    - It presents as high-grade fever, vomiting, watery diarrhea, sore-throat, hypotension, renal and heart failure, sunburned appearance (diffuse erythroderma), non-purulent conjunctivitis and desquamation which usually involves palms and soles.
    - Blood cultures may be negative.
- Food poisoning:
    - It is caused by ingesting toxins of Staphylococci in contaminated food. Toxins are resistant to heat of cooking.
    - There is development of vomiting, nausea, stomach cramps and diarrhea within 6 hours of ingestion of food.
- Scalded skin syndrome/ Ritter's syndrome:
    - Strains of bacteria release toxins called epidermolytic toxins A and B (exfoliatins).
    - Toxins bind to desmosomes and cause widespread red blistering of skin at the level of stratum corneum. Patients also have fever and irritability. Flaccid blisters rupture to release a moist red tender area (resembles scalded burns). Mucous membranes are spared in contrast to SJS/ TEN.

INVESTIGATIONS:

- CBC: reveal leukocytosis with left shift
- ESR, CRP: raised
- Blood or source cultures
- Relevant tests e.g. TEE for endocarditis

MANAGEMENT:

- Uncomplicated infections are treated with penicillinase resistant penicillins and cephalosporins e.g. dicloxacillin, cephalexin. Infections with MRSA require clindamycin, doxycycline, minocycline or trimethoprim-sulfamethoxazole.

- Complicated infections are treated with intravenous nafcillin, oxacillin, vancomycin, linezolid, daptomycin, tigecycline, telavancin or ceftaroline.
- Epidural abscess needs urgent antibiotics ± sugery to prevent neurological compromise.
- Toxic shock syndrome is managed by early recognition, antibiotic therapy, supportive therapy and removal of source of toxin.
- Food poisoning is managed with symptomatic and supportive treatment. Antibiotics are of no benefit.
- Scalded skin syndrome is managed with intravenous antibiotics and hydration. Corticosteroids should be avoided. Skin care with petroleum jelly.

3.6.5. COAGULASE NEGATIVE STAPHYLOCOCCAL INFECTIONS (CoNS)

- These include S. epidermidis, S. saprophyticus, S. haemolyticus, S. hominis, S. warnerii, S. saccharolyticus and S. cohnii. These are normal skin commensals and mostly associated with hospital-acquired infections related to prosthetic materials or foreign body.

PRESENTATION:

- S. epidermidis causes native valve endocarditis and infections of iv catheters and prosthetic implants e.g. prosthetic valve (endocarditis), vascular grafts, prosthetic joints (septic arthritis and osteomyelitis), pacemaker, peritoneal dialysis catheter, indwelling catheters.
- S. saprophyticus causes UTI in females with recent sex (honey-moon cystitis) and in patients with long-term foley's catheters.

MANAGEMENT:

- Remove infected source if possible. If removal is not feasible then treat with antibiotics. If antibiotics fail then it is mandatory to remove the source.
- Vancomycin is the treatment of choice as they are usually resistant to other classes.

⇨ ***Staphylococci are the most common cause of nosocomial infections***.

3.6.6. ENTEROCOCCAL INFECTIONS

BACTERIAL CHARACTERISTICS:

- Gram positive cocci occurring singly, in pairs or in short chains

PRESENTATION:

- Urinary tract infections
- Chronic prostatitis
- Native and prosthetic valve endocarditis
- Meningitis
- Surgical wounds
- Mixed intra-abdominal infections

INVESTIGATIONS:

- Culture of blood or source

MANAGEMENT:

- Beta-lactam and gentamicin in serious infections.
- Most of the enterococci especially E. faecium are inherently resistant to vancomycin (VRE or vancomycin resistant enterococci) and ampicillin.
- For E. faecium DAPTOMYCIN, QUINOPRISTIN/ DALFOPRISTIN, or LINEZOLID plus another active agent (DOXYCYCLINE with RIFAMPIN, TIGECYCLINE or a FLUOROQUINOLONE)

⇨ **Enterococci are the second most common cause of nosocomial infections (after staphylococci).**

3.6.7. CLOSTRIDIAL INFECTIONS

Bacterial characteristics:
These are all gram-positivespore-forming bacilli. There are different Clostridia namely:

1. Clostridium difficile – causes Clostridium difficile infection (CDI)
2. Clostridium botulism – causes botulism
3. Clostridium tetani – causes tetanus
4. Clostridium perfringens – causes gas gangrene

3.6.7.1. CLOSTRIDIAL DIFFICILE INFECTION (CDI)

Aka pseudomembranous colitis

"It is a nosocomial diarrheal infection caused by colonization of toxin-producing C. difficile."

QUICK FACTS: CLOSTIRIDUM DIFFICILE INFECTION	
Pathology:	**C. difficile colonizes large intestine → releases exotoxins → neutrophilic colitis, diarrhea, pseudomembranous colitis**
Presentation:	**Asymptomatic** **Watery diarrhea, abdominal cramps, nausea, anorexia, malaise**
Diagnosis:	**Stool for C. difficile toxin** **Sigmoidocolonoscopy** **Abdominal x-ray or CT scan**
Treatment:	**Iv hydration** **Oral metronidazole** **Oral vancomycin** **Iv fidaxmicin** **Fecal transplant** **Probiotics**

TRANSMISSION:

- Fecal-oral route by means of spores

PATHOGENESIS:

- C. difficile colonizes large intestine in susceptible patients (patients in whom normal flora has been depleted by use of antibiotics) → releases exotoxins (toxin A or enterotoxin and toxin B or cytotoxin)→ neutrophilic colitis and diarrhea → may form pseudomembranes in colon which can bleed or form pus.

RISK FACTORS:

- See Table 3.15.

Table 3.15. RISK FACTORS FOR DEVELOPMENT OF C. DIFFICILE INFECTION

- Current or recent history of intake of antibiotics (especially broad-spectrum antibiotics or prolonged courses)
- Elderly patients
- Immuno-compromised patients
- Patients receiving acid-suppression therapy (proton pump inhibitors)
- Hospitalization
- GI surgery
- Nursing home residence
- Inflammatory bowel disease

PRESENTATION:

- Asymptomatic (mostly)
- Watery diarrhea (usually mild to moderate, two to three stools per day; in severe cases frequent stools)
- Mild abdominal cramps

- Nausea, anorexia
- Malaise
- Dehydration
- In severe cases: fever, blood or pus in stools, abdominal tenderness

COMPLICATIONS:
- Dehydration, renal failure, toxic megacolon, intestinal perforation

INVESTIGATIONS:
- Stool for C. difficile toxin (enzyme immuno-assay OR glutamate dehydrogenase assay, PCR)
- Sigmoidocolonoscopy
- Imaging (e.g. abdominal x-ray, CT scan)

MANAGEMENT:
- IV hydration.
- For mild to moderate infections: oral METRONIDAZOLE 500 mg three times daily for 10 days.
- For severe and recurrent infections: oral VANCOMYCIN 125 – 500 mg four times daily for 10 days.
- If oral route not feasible: FIDAXOMICIN.
- Fecal microbiota transplant (stool transplantation).
- Probiotics like Saccharomyces boulardii as adjunctive treatment.
- Surgery in case of toxic megacolon or medically unresponsive infection.

⇨ ***Clostridium difficile is the most frequently reported nosocomial infection in developed countries.***

⇨ ***Suspect C. difficile infection in patients with diarrhea who have received antibiotics within last three months, have been recently hospitalized or develop diarrhea at least 48 hour after hospitalization.***

3.6.7.2. BOTULISM

"It is anacute neuromuscular condition caused by toxins of Clostridium botulinum."

QUICK FACTS: BOTULISM	
Pathology:	**C. botulinum toxins ingested or produced in wounds → anti-cholinergic action**
Presentation:	**Gastrointestinal symptoms → flaccid symmetrical descending paralysis (cranial nerves, upper limbs) → respiratory paralysis → lower limb paralysis**
Diagnosis:	**Toxin assay in serum or vomitus, stools or gastric fluid** **Toxin assay in food**
Treatment:	**Supportive treatment including intubation in respiratory failure** **Penicillin in wound botulism** **Botulinum anti-toxin**

CAUSATIVE AGENTS:
- Clostridium botulinum and rarely other clostridia

TRANSMISSION:
- Ingestion of spores in contaminated food or contamination of wounds by means of spores

PATHOGENESIS:
- Toxins (A, B, C1, D, E, F and G) ingested in food or produced by bacteria in wounds → disseminate hematogenously → anticholinergic action at nerve endings by either inhibiting acetylcholine release or binding to acetylcholine → hypotonia

PRESENTATION:
There are different types of botulism.
- Food-borne botulism:
  - Toxins ingested in food are resistant to digestion and get absorbed in blood.

  - Incubation period of 18 – 36 hours (sometimes longer).
  - It starts with acute gastrointestinal symptoms like nausea, vomiting and abdominal pain.
  - Patients develop descending symmetric flaccid paralysis which can lead to respiratory failure and death.
  - Weakness progresses as follows: cranial nerves, upper limbs, respiratory muscles, lower limbs.
  - Cranial nerve paralysis: diplopia, dysarthria, dysphonia, dysphagia, ptosis, dilated fixed pupils.
  - Autonomic involvement: dizziness, dry mouth
- Wound botulism:
  - There is history of traumatic wound with soil contamination.
  - After incubation period of 4 – 14 days, symptoms start.
  - It is similar to food-borne botulism except for less gastrointestinal symptoms.
- Intestinal botulism:
  - Clostridia colonize the intestine and produce toxins.
- Infant botulism:
  - Intestinal botulism in infants is called infant botulism.
  - Usually develops after ingesting contaminated honey.
  - Starts with constipation, weak cry and poor feeding and progresses to poor sucking

INVESTIGATIONS:

- Serum toxin bioassay
- Demonstration of C. botulinum or its toxin in vomitus, stools or gastric fluid
- Toxin assay in food
- Nerve conduction studies: NCV is normal, compound muscle action potential is decreased with maximal stimulus; facilitation is seen after repetitive stimulation at higher frequencies.

MANAGEMENT:

- Hospitalize patients with careful monitoring of oxygen saturation, respiratory rate and vital capacity.
- Consider intubation if impending respiratory failure.
- Antibiotics are of no use in food-borne botulism. Penicillins may be used in wound botulism along with wound debridement.
- Typically a bivalent anti-toxin (against toxin A and B) is used. A heptavalent botulism anti-toxin has been recently approved.

3.6.7.3. TETANUS

"It is a condition of hypertonia and generalized convulsions caused by C. tetani infection."

QUICK FACTS: TETANUS	
Pathology:	**C. tetani contaminates wounds and proliferates → releases toxin which inhibits release of inhibitory neurotransmitters (glycine and GABA) at pre-synaptic terminals → rigidity and hyperreflexia**
Presentation:	**Generalized tetanus: trismus, dysphagia, neck and back stiffness, abdominal rigidity, proximal limb stiffness** **Neonatal tetanus** **Cephalic tetanus**
Diagnosis:	**Clinical diagnosis** **EMG**
Treatment:	**Debridement of wounds** **Penicillin or metronidazole** **Alternatives: clindamycin, erythromycin** **Tetanus immunoglobulin** **Control seizures**

CAUSATIVE ORGANISMS:

- Clostridium tetani

TRANSMISSION:

- Infection is acquired by contamination of wounds with spores (e.g. deep puncture wounds,laceration).

PATHOGENESIS:

- Contamination of wounds with spores → bacteria proliferate → release tetanospasmin →travels up through peripheral motor neurons → migrates to presynaptic terminals →inhibits release of inhibitory neurotransmitters e.g. glycine and GABA → increased firing rates of α-motor neurons → rigidity and hyper-reflexia

PRESENTATION:

- Generalized tetanus:
  - Patients develop trismus (lockjaw) which is followed by dysphagia and stiffness or pain in neck, shoulder and back, abdominal rigidity, proximal limb muscle stiffness,
  - Risus sardonicus: sustained grimace or sneer due to contraction of facial muscles.
  - Ophisthotonus: arched back appearance due to contraction of muscles of back.
  - Some patients develop paroxysmal violent generalized spasms. Main threat is laryngospasm or apnea.
  - Autonomic dysfunction: sustained hypertension, tachycardia, hyperpyrexia, sweating,
- Neonatal tetanus:
  - It is seen in infants of unimmunized mothers and is usually generalized.
- Local tetanus:
  - Features are restricted to muscles near the wound.
- Cephalic tetanus:
  - It follows head injury or ear infection.
  - It involves one or more cranial nerves.

INVESTIGATIONS:

- Diagnosis is clinical.
- Leucocyte count and muscle enzymes may be elevated.
- EMG shows continuous motor discharges with shortening or absence of silent intervals.

MANAGEMENT:

- Admit patient in a quiet room in ICU.
- Maintain airway and breathing.
- Wounds should be cleaned and debrided.
- Give antibiotics: PENICILLIN 10 – 12 units iv for 10 days or METRONIDAZOLE 500 mg every 6 hours or 1 g twice daily
- For penicillin allergic patients CLINDAMYCIN and ERYTHROMYCIN are alternatives.
- Tetanus immunoglobulin (TIG) 3000 – 6000 units IM in divided doses.
- For controlling spasms: Benzodiaepines (e.g. DIAZEPAM, LORAZEPAM, MIDAZOLAM), CHLORPROMAZINE, barbiturates.
- Active immunization by tetanus toxoid.

3.6.7.4. GAS GANGRENE

Clostridial myonecrosis, Clostridial gas gangrene

"It is an infection of striated muscles caused by clostridia."

QUICK FACTS: GAS GANGRENE	
Pathology:	**C. perfringens, and other clostridia acquired → infect muscle cells and cause injury with minimal inflammation**
Presentation:	**Local pain, swelling, minimal or no inflammatory features** **Crepitus** **Watery discharge**

	Systemic features
Diagnosis:	**Increased muscle enzymes** **Gram stain and culture of discharge** **Bubbles in soft tissues on x-ray**
Treatment:	**Penicillin G, clindamycin, piperacillin-tazobactam, metronidazole, tetracycline**

CAUSATIVE ORGANISMS:

- Clostridium perfringens (formerly welchii)
- C. septicum
- C. hemolyticum

TRANSMISSION:

- By direct inoculation in muscles through wounds (prior trauma or surgery)
- Gall bladder and colonic surgery are particularly prone to gas gangrene

PATHOGENESIS:

- Bacteria proliferate in muscle → release toxins which directly cause injury (there is minimal inflammation) → also form gas in tissues which causes swelling and crepitus

PRESENTATION:

- Severe pain at the site with some swelling (minimal signs of inflammation)
- General signs: tachycardia, hypotension
- Local signs: edema, formation of blisters, severe tenderness, purplish black discoloration, crepitus in local tissue (due to local gas production), watery discharge
- Altered mental status (which improves as disease progresses).

INVESTIGATIONS:

- Increased muscle enzymes: LDH, aldolase, CPK
- Increased potassium
- CBC: may show raised neutrophils, anemia may occur due to intravascular hemolysis
- Examination and culture of discharge: shows clostridia with no white blood cells
- LFTs and renal function tests may be deranged
- X-rays may reveal fine gas bubbles in soft tissues
- Exploratory surgery and biopsy if diagnosis unclear

MANAGEMENT:

- Early diagnosis is crucial to save life and to save from amputation.
- Take surgical review for debridement.
- Administer supplemental oxygen.
- Give antibiotics: PENICILLIN G, CLINDAMYCIN, PIPERACILLIN-TAZOBACTAM, METRONIDAZOLE, TETRACYCLINE
- Role of hyperbaric oxygen therapy is unclear.

3.6.8. ANTHRAX

"It is a zoonosis caused by Bacillus anthracis."

QUICK FACTS: ANTHRAX	
Pathology:	**Bacillus anthracis survives in macrophages → migrates to lymph nodes → disseminate via blood**
Presentation:	**Cutaneous: pruritic papule → vesicle → ulcer with halo → malignant pustule → lymphadenopathy → systemic signs** **Inhalational: mediastinitis, necrotizing pneumonia** **Oropharyngeal and gastrointestinal disease, Meningitis**
Diagnosis:	**Gram stain and cultures of skin biopsy, pleural fluid, CSF or blood, Chest x-ray**
Treatment:	**Cutaneous anthrax: DOXYCYCLINE or quinolones or PENICILLIN** **Monoclonal antibodies: Raxibacumab or obiltoxaxiab** **Human anthrax immunoglobulins**

BACTERIAL CHARACTERISTICS AND TRANSMISSION:

- Bacillus anthracis: a gram positive bacillus
- Spores produced by bacteria survive in soil and animal hair. These are acquired by:
- Cutaneous contact (Contact with sick animal skins, hair and dead bodies or contact with fomites)
- Inhalation of spores
- Ingestion of contaminated meat

PATHOGENESIS:

- Spores germinate in macrophages → migrate to regional lymph nodes → proliferate → may cause bacteremia

PRESENTATION:

- Cutaneous:
  - Pruritic papule → forms a vesicle → ulcerates and is surrounded by an edematous halo → serosanguineous exudate with black exchar (malignant pustule) → local lymphadenopathy → systemic signs (fever, malaise, headache, myalgia, nausea, vomiting)
- Inhalational:
  - Can lead to hemorrhagic mediastinitis or rarely necrotizing pneumonia
- Oropharyngeal and gastrointestinal:
  - Edematous lesions (anywhere from oropharynx to cecum)→ necrotic ulcer → pseudomembrane formation → can bleed or cause local lymphadenopathy
  - In case of oropharyngeal disease: fever, sore-throat, neck swelling (due to soft tissue edema and cervical lymphadenopathy), dysphagia, respiratory distress, oral bleeding.
  - In case of GI disease: abdominal pain, fever, nausea, vomiting, malaise, hematemesis, bloody or watery diarrhea, shock.
- Meningitis

INVESTIGATIONS:

- Gram stain and culture of skin biopsy, pleural fluid, CSF or blood
- Chest x-ray: widened mediastinum, pleural effusion, normal parenchyma
- CT chest
- ELISA

MANAGEMENT:

- Cutaneous anthrax: DOXYCYCLINE or quinolones or PENICILLIN
- Monoclonal antibodies: Raxibacumab or obiltoxaxiab
- Human anthrax immunoglobulins

⇨ ***It is a potential biological weapon and was used in 2001 bioattack terrorism.***

3.6.9. DIPHTHERIA

"It is an infection caused by Corynebacterium diphtheria."

QUICK FACTS: DIPHTHERIA	
Pathology:	**Corynebacterium diphtheria adheres to epithelial cells and causes local inflammation, necrosis and releases exotoxins**
Presentation:	**Pharyngitis with pseudomembrane formation** **Cutaneous ulcers with grey membrane** **Cardiac toxicity: myocarditis, ECG changes, endocarditis** **Neurotoxicity: cranial nerve deficits, glove and stocking paresthesias**
Diagnosis:	**Gram stain** **Tellurite and Loeffler's media cultures**
Treatment:	**Erythromycin or penicillin; Anti-toxin**

CAUSATIVE ORGANISM:

- Corynebacterium diphtheria – a Gram positive aerobic bacillus

TRANSMISSION:

- Via respiratory droplets, nasopharyngeal secretions and fomites.
- Via contact with wound exudates

PATHOGENESIS:

- Adheres to epithelial cells → releases exotoxins → local inflammation and necrosis → hematogenous and lymphatic spread of toxins → affects heart, kidneys and nervous system

PRESENTATION:

- Pharyngeal:
  - Presents as sore-throat, low-grade fever, chills, malaise, weakness, prostration, headache, cervical lymphadenopathy, pseudomembrane formation in respiratory tract, hoarseness, dysphagia, dyspnea, stridor, wheeze.
- Cutaneous:
  - Presents as indolent non-healing ulcers with a grey membrane
- Cardiac toxicity presents as myocarditis, ECG changes (AV blocks, ST-T changes), endocarditis
- Neurotoxicity presents as cranial nerve deficits, glove and stocking paresthesias and peripheral neuritis.

INVESTIGATIONS:

- CBC shows leukocytosis
- Gram stain of sample shows club-shaped bacteria
- Cultures tellurite and Loeffler's media
- Tests for toxins including Elek test and PCR
- Tests for complications e.g. echocardiography

MANAGEMENT:

- Give antibiotics like erythromycin or penicillin
- Give diphtheria anti-toxin
- Repeat cultures in two weeks
- Prevention is possible by means of childhood vaccination

3.6.10. LISTERIOSIS

"It is an infection caused by Listeria monocytogenes."

QUICK FACTS: LISTERIOSIS	
Pathology:	**Listeria monocytogenes infection**
Presentation:	**General: gastroenteritis, bacteremia, meningitis or meningoencephalitis, endocarditis, septic arthritis** **Pregnant females: chorioamnionitis, pre-term labor and abortion** **Neonates: meningitis, sepsis**
Diagnosis:	**Blood cultures, CSF analysis and cultures**
Treatment:	**Ampicillin, gnetamicin**

BACTERIAL CHARACTERISTICS:

- Gram-positive non-spore forming facultative anerobic bacilli with characteristic tumbling motility.
- Also a siderophilic organism.

TRANSMISSION:

- Ingestion of contaminated food (particularly soft cheese, unpasteurized milk and dairy products)
- Trans-placental transmission
- Transmission during birth

PRESENTATION:

- Gastroenteritis:
  - Presents with diarrhea, fever, nausea, vomiting,
  - It is usually self-limiting.
- Bacteremia:
  - It presents with fever, myalgias, arthralgias, back-pain and head-ache.
- CNS infection:
  - Meningitis or meningoencephalitis: altered mental state, cranial nerve deficits, stroke-like syndrome, brain-stem encephalitis.
- In pregnant females:
  - It may cause chorioamnionitis, pre-term labour, spontaneous abortion, still-births
- In neonates:
  - Sepsis, meningitis
- Other infections:
  - Endocarditis, septic arthritis, osteomyelitis

INVESTIGATIONS:

- Blood cultures
- CSF examination:
  - Organisms may be seen on wet mount
  - Gram stain positive
  - Neutrophilic pleoctosis, increased CSF protein, decreased glucose
  - CSF cultures
- MRI brain

MANAGEMENT:

- Intravenous antibiotics e.g. ampicillin, gentamicin
- Symptomatic treatment

⇨ ***Listeria is a notorious cause of meningitis at extremes of age.***

3.6.11. NEISSERIA INFECTIONS

3.6.11.1. GONORRHEA

"It is a purulent infection of mucous membranes caused by Neisseria gonorrhea."

QUICK FACTS: GONORRHEA	
Pathology:	**Neisseria gonorrhea colonizes mucosa → purulent inflammation → spreads to other organs**
Presentation:	**Females: endo-cervicitis, PID** **Males: urethiritis, epididymitis, urethral stricture, prostatitis** **Disseminated infection: tenosynovitis, arthralgias, dermatitis, septic arthritis** **Neonates: ophthalmia neonatorum**
Diagnosis:	**Gram stain of discharge** **Culture with DNA probe and PCR**
Treatment:	**Ceftriaxone** **Spectinomycin, ciprofloxacin**

BACTERIAL CHARACTERISTICS:

- Neisseria gonorrhea: gram negative diplococcus

TRANSMISSION:

- It occurs by sexual contact or during child birth

PATHOGENESIS:

- After infection, bacteria colonize mucosal surfaces and cause purulent inflammation → retrograde spread to other organs→also may spread to blood stream to cause disseminated infection (gonococcemia)
- Many times gonococcus infection is associated with Chlamydia trachomatis co-infection.

PRESENTATION:

- In females:
  - It causes endo-cervicitis or pelvic inflammatory disease.
- In males:
  - It causes urethritis, epididymitis, urethral strictures, prostatitis, cystitis or rectal infection.
- Disseminated gonococcal infection:
  - It starts as tenosynovitis, arthralgias and dermatitis. It later progresses to septic arthritis and other complications like osteomyelitis, meningitis and endocarditis.
- In neonates:
  - Ophthalmia neonatorum: bilateral conjunctivitis after birth

INVESTIGATIONS:

- Gram stain of discharge shows gram negative diplococci within neutrophils
- Culture followed by DNA probe and then PCR assay

Management:

- Cephalosporin: drug of choice for most cases CEFTRIAXONE
- Alternatives: spectinomycin, ciprofloxacin

⇨ ***Gonococcemia is the most common cause of acute septic arthritis in young sexually active adults.***

3.6.11.2. MENINGOCOCCAL INFECTIONS

QUICK FACTS: MENINGOCOCCAL INFECTIONS	
Pathology:	**Neisseria meningitidis colonizes nasopharynx → reaches meninges and other organs via blood**
Presentation:	**Meningococcal meningitis** **Meningococcemia** **Water-house Fridrichsen syndrome**
Diagnosis:	**CSF analysis, cultures and PCR** **Blood cultures**
Treatment:	**Penicillin G** **Supportive measures**

BACTERIAL CHARACTERISTICS AND TRANSMISSION:

- Neisseria meningitidis: gram negative aerobic encapsulated diplococcus
- It is transmitted as air-borne droplets

PATHOGENESIS:

- Bacteria colonize nasopharynx → enter blood-stream and reach other organs like meninges → inflammatory products lead to endothelial necrosis, intraluminal thrombosis and perivascular hemorrhage.

PRESENTATION:

- Meningococcal meningitis:
  - Characteristics symptoms and signs of meningitis along with petechial, purpura or ecchymosis.
- Meningococcemia (dissemination of meningococci via blood-stream):
  - Skin shows petechiae, purpura, ecchymosis, etc.
  - Patients may have meningitis.
  - Fulminant meningococcemia includes fever, rash, shock and mucosal hemorrhages without meningitis.
  - Meningococcal septicemia presents as fever, rash, hypotension, multi-organ failure and altered level of consciousness.
  - Most severe form is Water-house Fridrichsen syndrome which is characterized by fever, purpura, DIC and adrenal insufficiency.

INVESTIGATIONS:

- General investigations:
  - CBC may show leukocytosis, thrombocytopenia
  - Raised D-dimers and fibrin degradation products
- CSF examination:
  - Increased opening pressure, neutrophilic leukocytosis, low glucose, increased protein
  - CSF gram stain and culture
  - PCR testing
- Imaging studies like CT or MRI brain with contrast
- Blood cultures

MANAGEMENT:

- Treatment of choice is penicillin G.
- Supportive treatment for other associations.

⇨ ***Neisseria meningitides is the most common cause of meningitis in adolescents and young adults and is the second most common cause of meningitis."***

3.6.12. PLAGUE

Aka Black Death

"Plague is a systemic zoonosis caused by Yersinia pestis."

QUICK FACTS: PLAGUE	
Pathology:	**Yersinia pestis transmitted by Xenopsylla cheopis → inflammation of regional lymph node → formation of bubo → spreads via lymphatics → causes shock and infects spleen, liver, meninges, lungs, etc.**
Presentation:	**Bubonic plague: systemic features + lymphadenitis + complications Primary septicemic plague: sepsis without lymphadenopathy Pneumonic plague: primary pneumonia with complications Other forms**
Diagnosis:	**Blood culture, Lymph node aspirate analysis, CSF analysis, F1 antigen testing**
Treatment:	**Streptomycin or gentamicin Alternatives: doxycycline, levofloxacin, moxifloxacin**

CAUSATIVE ORGANISM:

- Yersinia pestis: an oxidase negative, lactose-fermenting gram negative bacillus

TRANSMISSION:

- Bite of its vector, an infected rat flea (e.g. Xenopsylla cheopis)
- Handling of an infected rodents
- Respiratory droplets from infected rodents

PATHOPHYSIOLOGY:

- Bacteria replicate in regional lymph node → inflammation of lymph node (lymphocytic infiltration with thrombangitis obliterns and hemorrhagic necrosis and fibrin deposition) and inflammation of surrounding tissue → results in local swelling (Bubo) → disseminates via lymphatics to thoracic duct → septicemia and shock and spread to other organs (spleen, liver, secondary buboes, meninges, secondary plague pneumonia)
- Primary plague pneumonia occurs by inhalation (airway more involved than interstitium)

PRESENTATION:

1. Bubonic plague:
    a. Fever, malaise, myalgias, lymphadenitis presenting as buboes (usually inguinal)
    b. May disseminate to cause pneumonia and meningitis
2. Primary septicemic plague
    a. Septicemia without lymphadenopathy
3. Pneumonic plague
    a. Formed by direct inhalation of respiratory droplets.
    b. Fever, headache, myalgia, weakness are followed by cough, dyspnea, chest pain and hemoptysis.
4. Other forms include meningeal and pharyngeal plague.

INVESTIGATIONS:

- CBC shows neutrophilic leucocytosis, thrombocytopenia
- Blood cultures
- Analysis of lymph node aspirate
- CSF analysis
- F1 antigen testing by direct immunofluorescence or passive hemagglutination

MANAGEMENT:

- Patients with pneumonia should be isolated.
- Hydrate patients aggressively.

- Vasopressors should be started for fluid refractory hypotension.
- STREPTOMYCIN or GENTAMICIN is the treatment of choice.
- Alternative treatments include DOXYCYCLINE, LEVOFLOXACIN and MOXIFLOXACIN.

3.6.13. VIBRIO INFECTIONS

3.6.13.1. CHOLERA

CAUSATIVE ORGANISMS:
- Vibrio cholerae serogroups O1and O139

PRESENTATION:
- Spread by fecal contamination of edibles and water → Incubation period of 24 – 48 hours → profuse watery diarrhea (rice water stools) and vomiting → can lead to severe dehydration and death

INVESTIGATIONS:
- Stool cultures on special media

MANAGEMENT:
- Rapid rehydration with WHO reduced osmolarity ORS
- Single dose of antibiotic DOXYCYCLINE, CIPROFLOXACIN, AZITHROMYCIN.

3.6.13.2. VIBRIO PARAHEMOLYTICUS

- Infection spreads by drinking contaminated seawater or eating under-cooked seafood.
- Patients develop watery diarrhea, nausea, abdominal cramps and fever.

3.6.14. AEROMONAS INFECTIONS

BACTERIAL CHARACTERISTICS:
- Gram negative,oxidase positive, facultative anerobic bacilli

TRANSMISSION:
- Fecal-oral transmission

PRESENTATION:
- Gastroenteritis
    - It occurs in children and immuno-compromised as either watery diarrhea or dysentery.
- Septicemia
- Skin and soft tissue infections:
    - Cellulitis, myonecrosis and necrotizing fasciitis
- Other infections including ocular disease, respiratory tract infections, urinary tract infections, bone and joint infections

INVESTIGATIONS:
- Isolation in stool or blood

MANAGEMENT:
- Antibiotics like aminoglycosides, newer generation cephalosporins, carbapenems, macrolides and quinolones.

3.6.15. SALMONELLA INFECTIONS

3.6.15.1. ENTERIC FEVER

QUICK FACTS: ENTERIC FEVER	
Pathology:	**Bacteria reach distal ileum → infect Peyer patches → carried via lymphatics to thoracic duct → spread to reticuloendothelial organs and gall bladder**
Presentation:	**Week 1: high-grade fever (classically step-ladder pattern), abdominal pain, constipation, cough** **Week 2: previous symptoms increase, splenomegaly, relative bradycardia, dicrotic pulse** **Week3: toxic look, weight loss, tachypnea, diarrhea, typhoid state, complications**
Diagnosis:	**Clinical diagnosis** **Blood cultures, stool cultures** **IgM, IgG**
Treatment:	**First line: cefixime** **Alternatives: azithromycin, ciprofloxacin** **Complicated cases: ceftriaxone, aztreonam, imipenem** **Dexamethasone in complicated cases**

CAUSATIVE AGENTS:

- Salmonella enterica (serovars typhi and paratyphi A, B and C)

INCUBATION PERIOD:

- 10 – 14 days

PATHOPHYSIOLOGY:

- Bacteria ingested → reach distal ileum→reach Peyer patches and are engulfed by phagocytic cells → present to macrophages in lamina propria →incite inflammation → carried to thoracic duct via mesenteric lymph nodes → spread to reticulo-enodthelial tissues in liver, spleen, bone marrow and lymph nodes → infect gall bladder and are secreted in bile → re-enter distal ileum and cycle continues.

PRESENTATION:

- Week 1:
  - High-grade fever: rises during day and drops by morning; each day fever peaks and troughs are higher than yesterday (step-ladder pattern).
  - Gastrointestinal features: diffuse abdominal pain and tenderness, right upper quadrant colicky pain, constipation
  - Dry cough, headache, delirium, malaise
  - Coated tongue
- Week 2:
  - Fever plateaus around 103 – 104 degree F.
  - Rose spots: salmon-colored, maculopapular rash on torso
  - Abdominal distension
  - Soft splenomegaly
  - Relative bradycardia (pulse rate does not rise according to temperature)
  - Dicrotic pulse
- Week3:
  - Toxic look, anorexia
  - Weight loss
  - Tachypnea
  - Thready pulse
  - Pea-soup diarrhea (foul-smelling greenish-yellow)

    - Typhoid state: apathy, confusion, psychosis
    - Complications: bowel perforation, peritonitis, myocarditis, GI hemorrhage
    - Death usually occurs if untreated.
- Week 4:
    - Survivors may become carriers.
- Atypical presentations:
    - Fever with diarrhea from onset
    - Meningismus or meningitis
    - Acute lobar pneumonia
    - Arthralgias
    - Severe jaundice
    - GBS
    - Pancreatitis
    - Orchitis
    - Osteomyelitis
    - Abscesses
    - Urinary retention, nephritis, hematuria

INVESTIGATIONS:

- Diagnosis is clinical
- CBC: anemia, thrombocytopenia, lymphopenia
- ESR: raised
- PT, APTT: deranged
- LFTs: mildly raised
- ALT to LDH ratio of more than 9:1: differentiates typhoid from viral hepatitis
- Bone marrow cultures (best yield but paiful)
- Blood cultures (clinically best)
- Cultures of vomitus, duodenal aspirate or stools
- Widal test: measures agglutinating antibodies against H an O antigens (NOT USEFUL)
- IgM or IgG (variable)
- Histology: macrophage aggregates (typhoid nodules)

MANAGEMENT:

- Antibiotics
    - Fluoroquinolones e.g. CIPROFLOXACIN 500 mg 12 hourly for 14 days. Resistance has widely emerged. GATIFLOXACIN is promising.
    - Uncomplicated cases:
        - CEFIXIME 10 – 20 mg/ kg/ day in two divided doses for 12 days.
        - Alternatives: AZITHROMYCIN 500 mg once daily for 2 weeks.
    - Complicated cases:
        - CEFTRIAXONE
        - Alternatives: AZTREONAM, IMIPENEM
    - Other options: trimethoprim-sulfamethoxazole, ampicillin, oflaxacin
- Dexamethasone: decreases mortality in severe complicated cases howevere may mask symptoms
- Symptomatic relief: anti-pyretics, hydration

⇨ ***Classical presentation of enteric fever is tetrad of fever, malaise, abdominal pain and constipation.***

3.6.16. SPIROCHAETAL INFECTIONS

Table 3.16. CLASSIFICATION OF SPIROCHAETES	
AEROBIC SPIROCHAETES	
Leptospira	Leptospirosis
ANAEROBIC SPIROCHAETES	
Borrelia	Borreliosis
Treponema	Syphilis, yaws, bejel, pinta

3.6.16.1. LEPTOSPIROSIS

"Leptospirosis is a zoonosis caused by leptospira."

QUICK FACTS: LEPTOSPIROSIS	
Pathology:	**Leptospira infection → affects liver, kidneys and lungs, and causes DIC**
Presentation:	**Anicteric (mild) disease: fever, chills, rigors, abdominal pain, headache, retro-orbital pain, complications (meningitis, uveitis, pneumonia)** **Incteric (severe) disease (Weil's disease): renal failure, liver failure, meningitis, hemorrhagic pneumonia, shock, DIC, HUS-TTP**
Diagnosis:	**Leptospira serology** **DNA PCR** **Microagglutination test** **Culture**
Treatment:	**Doxycycline, ampicillin, amoxicillin, macrolides, fluoroqunolones** **Supportive treatment**

BACTERIAL CHARACTERISTICS:

- Gram negative coiled motile organisms
- Pathogenic Leptospira species are Leptospira interrogans which has many serovars including L. icterohemorrhagiae.

TRANSMISSION:

- Contact of skin abrasions or mucosal surfaces with urine and excreta of rats, dogs, cattle and pigs e.g. sewage workers, swimming or diving in contaminated water.
- Drinking water contaminated with urine of reservoirs.

PATHOPHYSIOLOGY:

- Incubation period of 5 – 14 days → lymphocytic capillary vasculitis
- In kidneys: interstitial nephritis and tubular necrosis
- In liver: centrilobular necrosis
- In lungs: alveolar hemorrhage
- Shock/ DIC/ HUS-TTP may develop

PRESENTATION:

The disease can range from a mild anicteric disease to severe disease (Weil's disease)
In anicteric leptospirosis (mild form):

- Leptospiremic/septicemic phase: occurs for 3 – 14 days and patients develop fever, chills, rigors, abdominal pain, headache, retro-orbital pain, photophobia, myalgias
- Improvement phase: 1 – 3 days symptom free period
- Immune phase: meningitis, uveitis, hemorrhagic pneumonia may occur

Icteric leptospirosis/ Weil's disease (most severe form):

- Renal failure due to ATN or AIN
- Liver failure
- Meningitis
- Hemorrhagic pneumonia

- Shock
- DIC/ HUS-TTP

Investigations:
- General investigations may reveal anemia, neutrophilia with left shift, thrombocytopenia, hyperbilirubinemia, raised urea and creatinine and raised hepatic enzymes.
- Leptospira IgM or IgG ELISA for screening purposes
- IgM titers ≥1:2000 or a four-fold rise in acute and convalescent serum samples.
- DNA PCR of blood, urine, CSF or tissue samples
- Microscopic agglutination test (MAT)
- Culture in specific media

TREATMENT:
- In mild cases: disease is self-limited and needs no treatment.
- Antibiotics
    - In non-hospitalized patients: doxycycline, ampicillin, amoxicillin, macrolides, fluoroquinolones.
    - In hospitalized patients: penicillins, third generation cephalosporins, or iv erythromycin.
- Supportive treatment for organ failure and shock.

⇨ ***Leptospirosis is the most common zoonosis in the world.***

3.6.16.2. LYME DISEASE

"Lyme disease is caused by Borrelia burgdorferi."

QUICK FACTS: LYME DISEASE	
Pathology:	**Borrelia burgdorferi acquired by bite of Ixodes tick**
Presentation:	**Stage 1: erythema migrans** **Stage 2: systemic features, meningitis, encephalitis, cranial neuritis including facial diplegia, radiculoneuropathy, mononeuritis multiplex, ataxia, myelitis** **Stage 3: large joint oligoarthritis, encephalopathy, peripheral neuropathy, acrodermatitis chronic atrophicans** **Chronic lyme disease: chronic fatigue syndrome**
Diagnosis:	**Acute and convalescent phase serology** **Joint aspirate PCR**
Treatment:	**Doxyxycline, amoxicillin, cefuroxime, erythromycin**

BACTERIAL CHARACTERISTICS:
- Borrelia burgdorferi is a fastidious micro-aerophilic spirochete.

TRANSMISSION:
- By bite of Ixodes tick

CLINICAL MANIFESTATIONS:
- STAGE 1 (LOCALIZED INFFECTION):
    - A red macule develops at the bite site that expands slowly into an annular lesion with a bright red outer border and a central clearing. This lesion is called erythema migrans.
- STAGE 2 (DISSEMINATED INFECTION):
    - After few days to weeks disseminated features appear.
    - Non-specific symptoms like headache, neck stiffness, fever, chills, migratory musculoskeletal pain, arthralgias, malaise and fatigue.
    - Neurologic deficits like meningitis, encephalitis, cranial neuritis including bilateral facial nerve palsy, motor or sensory radiculoneuropathy, mononeuritis multiplex, ataxia, myelitis, lymphocytic pleocytosis, etc.
    - Cardiac features like fluctuating atrioventricular block and acute myopericarditis.
- STAGE 3 (PERSISITENT INFECTION):
    - Untreated patients may develop rheumatologic or neurologic features.

  - Intermittent attacks of large-joint oligo-arthritis especially of knees.
  - Encephalopathy, peripheral neuropathy
  - "Acrodermatitis chronica atrophicans/ Herxheimer disease" is appearance of localized cutaneous swellings with progressive allodynia (exaggerated response to pain) with Borrelia afzelli infection.
- CHRONIC LYME DISEASE:
  - A syndrome similar to chronic fatigue syndrome is noted for years after the initial infection. It is also called as post-treatment Lyme disease syndrome (PTLDS).

DIAGNOSIS:
- Acute and convalescent-phase serologic tests
- PCR of joint fluid

TREATMENT:
- Doxycycline 100 mg BD (drug of choice)
- Alternatives include AMOXICILLIN 500 mg TDS, CEFUROXIME 500 mg BD, ERYTHROMYCIN 250 mg QID, etc.
- The drugs are taken for 14 days in case of localized infection and for 21 days in case of disseminated one.
- Intravenous drugs are indicated in case of neurologic involvement, third degree AV block and failure of treatment with oral agents.
- Arthritis is treated with DOXYCYCLINE for 30 days.

PROPHYLAXIS:
- Single dose of DOXYCYCLINE 200 mg

⇨ ***Lyme disease is the most common vector-borne disease in the United States.***

3.6.16.3. SYPHILIS

"It is an infectious venereal disease caused by Treponema pallidum."

QUICK FACTS: SYPHILIS	
Pathology:	**T. pallidum infects endothelial cells and different organs → obliterative endarteritis and plasma cell rich infiltrates**
Presentation and examination:	**Primary syphilis: painless chancre** **Secondary syphilis: systemic symptoms, maculopapular rash involving palms and soles, condyloma lata** **Latent syphilis: persistent seroreactivity after secondary syphilis** **Tertiary syphilis: gummas in liver, bones and testes, neurosyphilis (meningitis, encephalitis, tabes dorsalis, general paresis), cardiovascular syphilis (aortitis, AR, aneurysms)** **Congenital syphilis: snuffles, sabre tibia, saddle nose, Clutton's joints, Hutchinson's teeth, mulberry molars**
Diagnosis:	**Non-treponemal serology: VDRL, RPr, ICE** **Treponemal serology: FTA-ABS, MHA-TP, TPHA** **Darkfield microscopy of moist lesions** **CSF analysis, VDRL, FTA**
Treatment:	**Penicillin, doxycycline, erythromycin, ceftriaxone**

TRANSMISSION:
- Sexual contact with infected lesions
- Trans-placental transmission from mother to fetus
- Transfusion of infected blood products
- Contact of skin breaks with infected lesions

- Transplantation of infected organs

PATHOPHYSIOLOGY:

- Treponemes bind to endothelial cells → endarteritis → heals with scarring → obliterative endarteritis
- In different organs treponemes → delayed type hypersensitivity → plasma cell rich infiltration
- In tertiary syphilis: formation of gummas (central necrosis surrounded by palisading macrophages, lymphocytes and plasma cells)

STAGES OF SYPHILIS:

1. *Primary syphilis:* After an incubation period of 3 – 6 weeks primary lesion appears
    a. Painless chancre (a highly infectious red papules that erode to form punched-out ulcer with rolled edges) appears at area of sexual contact (glans penis, vulva, cervix, anus, fingers etc.). It heals within 3 – 12 weeks with or without treatment.
2. *Secondary syphilis:* 4 – 10 weeks after primary lesion, spirochetes further disseminate and lead to following:
    a. Systemic features: fever, malaise, myalgias, arthralgias, lymphadenopathy
    b. Rash: typically maculopapular and involves palms and soles.
    c. Condyloma lata: greyish-white painless infectious lesions at warm moist areas
    d. Patchy alopecia
3. Latent syphilis:
    a. This is persistent sero-reactivity despite resolution of secondary syphilis.
4. Tertiary syphilis: 1/3 of latent syphilis patients develop tertiary syphilis.
    a. Gummatous syphilis/ late benign syphilis: gummas form in liver, bones and testes.
    b. Neurosyphilis:
        i. Meningeal syphilis: chronic meningitis
        ii. Meningovascular syphilis: subacute encephalitis
        iii. Parenchymatous syphilis:
            1. Tabes dorsalis: demyelination of posterior columns, dorsal roots and dorsal root ganglia which lead to ataxia, wide-based gait, loss of position, deep pain and temperature sensations and areflexia.
            2. General paresis: disorders of personality and affect, hyper-reflexia, Argyll Robertson pupil in eye, intellectual decline and loss of speech.
    c. Cardiovascular syphilis: there is obliterative endarteritis of vasa vasorum → aortitis, aortic regurgitation, saccular aneurysm and coronary ostial necrosis.

5. *Congenital syphilis:* Syphilis may cross placenta and cause spontaneous abortion and stillbirths. Survivors develop the features of secondary syphilis with widespread condyloma lata and rash.
    a. Snuffles: mucopurulent rhinitis
    b. Saddle nose: destroyed nasal septum
    c. Sabre tibia: inflammation and bowing of tibia
    d. Clutton's joints: knee joints
    e. Hutchinson's teeth: widely spaced notched upper incisors
    f. Mulberry molars: too many cusps on molars

INVESTIGATIONS:

- Non-treponemal serological testing: VDRL, RPR, ICE syphilis recombinant antigen testing
- Treponemal serological testing: Fluorescent treponemal antibody-absorption (FTA-ABS), microhemagglutination assay for T. pallidum (MHA-TP), T. pallidum hemagglutination (TPHA), T pallidum particle agglutination (TPPA), Treponemal enzyme immunoassay (TEIA).
- Dark field microscopy of moist lesions
- For neurological features: CSF exam shows high cell counts with lymphocyte predominance, low glucose and high proteins. CSF VDRL and CSF FTA may be performed.
- Check for concomitant HIV infection.

MANAGEMENT:

- Treatment is penicillin (drug of choice).
- If penicillin allergy is present then alternatives are doxycycline, erythromycin and ceftriaxone.

- Check for response to treatment by using VDRL or RPR at 6 and 12 months in primary and secondary syphilis and at 6, 12 and 24 months in tertiary syphilis.

⇨ ***Jarisch-Herxheimer reaction: it is an inflammatory reaction to dying treponemal antigens which occurs on initiation of therapy. It consists of fever, myalgias, headache and tachycardia. Management is symptomatic.***

3.6.16.4. YAWS

"It is an endemic treponematosis caused by Treponema pallidum pertenue."

TRANSMISSION:
- By direct contact

CLINICAL MANIFESTATIONS:
- Primary yaw: A papule (mother yaw) develops at the inoculation site and may undergo secondary changes. Regional lymphadenopathy is also seen.
- Secondary yaw: Disseminated skin and bone lesions along with constitutional symptoms appear.
- Tertiary yaw: Destructive gummatous skin and bone lesions develop in this stage.

TREATMENT:
- BENZATHINE PENICILLIN or DOXYCYCLINE

3.6.16.5. BEJEL (ENDEMIC SYPHILIS)

"It is an endemic treponematosis caused by Treponema pallidum endemicum."

TRANSMISSION:
- By direct contact

CLINICAL MANIFESTATIONS:
- An intra-oral papule develops which is followed by oral mucous and mucocutaneous lesions. Late destructive gummatous may develop.

TREATMENT:
- BENZATHINE PENICILLIN or DOXYCYCLINE

3.6.16.6. PINTA

"It is an endemic treponematosis caused by Treponema pallidum carateum."

TRANSMISSION:
- By direct contact

CLINICAL MANIFESTATIONS:
- Pinta is benign and the lesions are confined to skin only.
- There is development of flat, itchy red areas which undergo different changes in texture and color.

TREATMENT:
- BENZATHINE PENICILLIN or DOXYCYCLINE

3.6.17. MYCOBACTERIAL INFECTIONS

3.6.17.1. TUBERCULOSIS

"It is a chronic multi-systemic debilitating infection caused by Mycobacterium tuberculosis complex (M. tuberculosis and M. bovis."

QUICK FACTS: TUBERCULOSIS	
Pathology:	**M. tuberculosis transmitted by aerosols → inhaled and lodges in alveoli → survives inside macrophages → spreads to regional lymph nodes →granulomatous inflammation around foci → infection contained**
Presentation:	**Primary TB: middle and lower lobes of lungs with lymphadenopathy** **Latent TB: dormant infection detected by PPD or IGRA** **Post-primary/ progressive TB: cavitation, effusion or dissemination after primary infection** **Secondary TB/ reactivation: upper lobe involvement with fever, cough, weight loss, malaise, night-sweats, sputum** **Military TB: disseminated TB involving lung in military pattern, choroid, meninges, liver, spleen** **Extra-pulmonary TB: lymph nodal, pleural, genitourinary, skeletal, central nervous or peritoneal TB**
Diagnosis:	**Specimen from involved site: AFB smear, AFB cultures, PCR** **Imaging tests: chest x-ray, CT scan**
Treatment:	**First-line anti-tuberculous therapy: isoniazid + rifampicin + ethambutol + pyrazinamide along with vitamin B6** **Group 4 – 5 ATT for MDR and XDR TB**

CAUSATIVE ORGANISM:

- M. tuberculosis is an acid-fast aerobic bacillus.
- **Multi-drug resistant TB (MDR TB):** TB resistant to both isoniazid and rifampicin.
- **Extremely-drug resistant TB (XDR TB):** TB resistant to isoniazid, rifampicin, fluoroquinolones and at least one injectable drug (amikacin, kanamycin or capreomycin).

RISK FACTORS FOR TB:

- Immigrants from endemic areas, residing in crowded areas, health-care workers with exposure to TB, close contacts of patients with TB, HIV/AIDS, Immunosuppression (including diseases as well as drugs which suppress immune response e.g. long-term steroids, TNF antagonists), uncontrolled diabetes mellitus, chronic renal failure, malnutrition, post-transplant patients, alcoholism, cancer, gastrectomy, elderly patients, silicosis.

RISK FACTORS FOR MDR TB:

- Previous TB treatment, inadequate TB treatment, HIV, diabetes mellitus, close contact with MDR TB patients, residing in a region where there is high prevalence of MDR TB

TRANSMISSION:

- Via inhalation of aerosolized droplets from infected person
- Via ingestion of unpasteurized milk (M. bovis)

PATHOPHYSIOLOGY:

- AFB inhaled → reach alveoli → ingested by macrophages and survive inside → spread to regional lymph nodes (Ghon complex) → contained via granulomas → resolution of primary infection → mycobacteria remain dormant in granulomas → may reactivate later

PRESENTATION:

- Primary tuberculosis pneumonia:
    - It usually occurs in middle and lower lobes along with regional lymphadenopathy.
    - It usually heals spontaneously in immuno-competent patients and forms Ghon lesion.

    - In immuno-suppressed patients, disease may form cavitation, pleural effusion or disseminated disease. This is known as post-primary TB or progressive TB.
    - In 5 – 10% of patients, the disease may reactivate at any point in life.
- Latent TB:
    - It is term used for dormant TB infection.
    - Latent TB can reactivate later in life.
    - It is detected by PPD or IGRA.
    - Active TB should be excluded in all patients by performing chest x-ray or sputum examination.
- Secondary TB/ Reactivation of pulmonary disease:
    - It occurs when host immunity is weakened.
    - It usually occurs in apical or posterior segments of upper lobe.
    - It presents as fever, night sweats, weight loss, malaise and dry cough (may form sputum or hemoptysis).
    - It can spread via blood or lymphatics.
- Miliary TB:
    - It is widespread dissemination of tuberculosis via hematogenous spread.
    - Patients develop weakness, weight loss, fatigue, low-grade fever, headache, cough, organomegaly, choroidal tubercles in eye, etc.
    - It appears as millet-seed like nodules spread in lung fields on chest x-ray.
    - 25% of patients have meningeal involvement.
- Extra-pulmonary TB:
    - Lymphadenitis/ scrofula
    - Pleural tuberculosis
    - Genitourinary tuberculosis
    - Skeletal disease: Pott disease, tuberculous arthritis
    - CNS tuberculosis: manifests as chronic meningitis, tuberculoma or tubercular brain abscess.
    - Gastrointestinal tuberculosis
    - Peritoneal tuberculosis
    - Pericarditis

INVESTIGATIONS:

- CBC: leucopenia or leukocytosis
- ESR: usually raised
- Light microscopic examination of Ziehl-Neelsen fuschin staining or fluorescent microscopic examination of Auramine-rhodamine staining of AFB bacilli.
- Cultures of specimen from involved site: sputum, blood, urine, CSF, etc.
- Histopathology of involved tissues: lymphocytic predominant inflammation with formation of granulomas which may have central caseous necrosis.
- Pulmonary TB:
    - Sputum AFB smear and culture
    - At least two samples of sputum should be sent: one immediately and one early morning sputum sample.
    - If sputum sample not expectorated, then induce with steam, nebulization with normal saline and chest physiotherapy.
    - If still no sputum obtained then consider early morning gastric wash samples or broncho-alveolar lavage.
    - Sputum cultures in solid (LJ medium) or liquid media (BACTEC).
    - Pleural biopsy can also be done.
- Meningeal TB: CSF examination forlymphocytic pleocytosis, raised proteins, low glucose, AFB smear and cultures; CT or MRI brain with contrast
- Lymphatic TB: lymph node biopsy
- Mantoux/ tuberculin skin test with purified protein derivative (PPD): tests immunity against M. TB and thus past infection. It is only useful to diagnose latent TB.
- Interferon gamma release assay (IGRA): it is a blood test to detect TB infection (does not differentiate between latent and active TB).

- Nucleic acid probes with PCR
- Xpert MTB/ Rif assay: used to screen for MDR TB and also to diagnose TB
- Imaging tests e.g. chest x-ray, CT chest, ultrasound abdomen, CT abdomen
- Consider sending HIV serology if relevant.

Table 3.17. FIVE CLASSES OF ANTI-TUBERCULOUS DRUGS

GROUP 1 FIRST-LINE ORAL	GROUP 2 SECOND-LINE INJECTABLE	GROUP 3 FLUORO-QUINOLONES	GROUP 4 ORAL BACTERIO-STATIC	GROUP 5 UNCLEAR DRUGS
Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin	Kanamycin Amikacin Capreomycin Streptomycin	Levofloxacin Moxifloxacin Ofloxacin Gatifloxacin	Para-aminosalicylic acid Cycloserine Terizidone Ethionamide Prothionamide	Clofazimine Linezolid Amoxicillin-clavulanate Thiacetazone Clarithromycin Imipenem-cilastatin High dose isoniazid

Table 3.18. PROFILE OF FIRST-LINE ANTI-TUBERCULOUS AGENTS

	ISONIAZID	RIFAMPICIN	ETHAMBUTOL	PYRAZINAMIDE
Dose	5 mg/kg (not more than 300 mg/day)	10 mg/ kg / day	15 – 25 mg/kg/ day (20)	20 – 30 mg/ kg / day (25)
Mechanism of action	Peroxidative action inhibits lipid and nucleic acid biosynthesis (Bactericidal)	Inhibition of bacterial DNA-dependent RNA polymerase (Bactericidal)	Inhibits arabinosyl transferase which polymerizes arabinose into arabinan for cell wall synthesis (Bacteriostatic)	Activates to pyrazinoic acid inside mycobacteria to inhibit fatty acid synthesis (Low bactericidal)
Side-effects	Peripheral neuropathy, hepatotoxicity, drug induced SLE	Reddish discoloration of bodily secretions, severe thrombocytopenia, hepatitis P450 inducer	Optic neuritis/ color vision disturbance	Hepatotoxicity, nausea, vomiting, hyperuricemia

MANAGEMENT:

- For latent tuberculosis isoniazid is given for 9 months after excluding active TB. This includes patients with positive PPD testing.
- For active tuberculosis:
    - First-line anti-tuberculous therapy for new patients – Rifampin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z). All four drugs are given for first two months (intensive phase) while only isoniazid and rifampicin are given for next four months (maintenance phase).
    - First-line anti-tuberculous therapy for previously treated patients: HRZE + streptomycin for 3 months followed by HRE or HR for 5 months.
    - Treatment is given for nine months in case of osteomyelitis, military TB, meningitis, pregnancy or if pyrazinamide is not used.
    - Give PYRIDOXINE 100 mg daily for patients at high risk for isoniazid-induced peripheral neuropathy.
    - Glucocorticoids are given in case of pericardial TB or CNS TB.
    - Check sputum samples at 2^{nd}, 5^{th} and 6^{th} month for new cases and at 3^{rd}, 5^{th} and 8^{th} month for previously treated cases.
    - Isolate smear positive TB cases for at least one month of starting treatment or until three consecutive sputum smears are negative.
- Special circumstances:
    - Renal failure: reduce dose of ethambutol and pyrazinamide to three times weekly instead of daily dosing. Give doses after hemodialysis if dialysis-dependent or half dose daily.
    - Pregnancy: do not use PYRAZINAMIDE or STREPTOMYCIN.
    - Chronic liver disease: PYRAZINAMIDE is not given so duration of treatment is longer. Hepatotoxicity should be monitored.
- For MDR TB use one susceptible injectable and at least 3 additional susceptible oral drugs from following:
    - Aminoglycosides: streptomycin, amikacin, capreomycin, kanamycin

- Fluoroquinolone: levofloxacin, ciprofloxacin, ofloxacin
- Thioamide: ethionamide, prothionamide
- Pyrazinamide
- Ethambutol
- Cycloserine
- Terizidone
- Para-amino salicylic acid
- Rifabutin
- Diaarylquinoline: bedaquiline

⇨ ***Lymph nodes are most common site for extra-pulmonary tuberculosis (35%).***

Table 3.19. REQUIREMENTS FOR INTERPRETATION OF PPD TEST AS POSITIVE		
5 – 10 mm	**10 – 15 mm**	**> 15 mm**
HIV-positive patients Glucocorticoid use Close contact with active TB Abnormal calcifications Organ transplant recipients	Recent immigration (within 5 years) Prisoners Health-care workers Close contact of someone with TB Hematologic malignancy Alcoholics Diabetes mellitus	People with no risk factors

3.6.17.2. LEPROSY

Aka Hansen's disease

"It is a chronic infection caused by mycobacterium leprae which causes sensory or sensorimotor neuropathy."

QUICK FACTS: TUBERCULOSIS	
Pathology:	**M. lepra infects Schwann cells → demyelination + granulomatous inflammation**
Presentation:	**Tuberculoid form: one or few dry hypoaesthetic itchy skin patches** **Lepromatous form: multiple nodules or plaques with intact sensation + thickened nerves, deformities due to nerve damage**
Diagnosis:	**NCS, skin biopsy, serology**
Treatment:	**Paucibacillary single lesion: rifampicin, ofloxacin or minocycline.** **Paucibacillary >1 lesion: dapsone + rifampicin 600 mg** **Multibacillary: dapsone + clofazimine + rifampicin**

PATHOPHYSIOLOGY:

- M. leprae acquired via droplets → infects Schwann cells and causes demyelination → also causes inflammatory reaction and granuloma formation.
- It affects the skin, peripheral nerves, upper respiratory mucosa and eyes.

It presents in two major forms:

- Tuberculoid leprosy:
  - It occurs in patients with intact immunity.
  - There is minimal skin involvement (dry hypoaesthetic lesions without AFB on smear).
- Lepromatous leprosy:
  - It occurs in patients with immunocompromised status.
  - There is extensive skin involvement (nodules or plaques with abundant AFB on smear)

PRESENTATION:

- Painless but itchy skin patches in tuberculoid leprosy (nodules or plaques with intact sensations in lepromatous leprosy)
- Loss of sensations or paraesthesias in affected peripheral nerves
- Palpable nerves e.g. ulnar or posterior tibial
- Wasting and muscle weakness
- Deformities e.g. foot drop, claw hands

- Leonine facies, saddle-nose deformity

INVESTIGATIONS:

- NCS: axonal and demyelinating sensory or sensorimotor neuropathy
- Skin biopsy
- Serologic assays

MANAGEMENT:

- Paucibacillary single lesion: single dose of RIFAMPICIN, OFLOXACIN or MINOCYCLINE.
- Paucibacillary >1 lesion: DAPSONE 100 mg orally once daily, RIFAMPICIN 600 mg orally once monthly for 6 months.
- Multibacillary: DAPSONE 100 mg orally once daily, CLOFAZIMINE 50 mg orally once daily or 300 mg once monthly, RIFAMPICIN 600 mg orally once monthly.

3.7. PROTOZOAL INFECTIONS

3.7.1. MALARIA

"It is a blood-borne parasitic infection caused by Plasmodium species."

QUICK FACTS: MALARIA	
Pathology:	**Infected female anopheles bites humans → sporozoites enter blood and reach liver → form merozoites and released in blood again → multiply in red blood cells which eventually rupture and release merozoites**
Presentation:	**Acute: Paroxysmal high-grade fever with chills, rigors, headache, sweating, cough, fatigue, anemia, splenomegaly, jaundice, occasionally hepatomegaly Chronic: tropical splenomegaly, quartan malarial nephropathy**
Diagnosis:	**CBC: anemia, thrombocytopenia Peripheral smear: malarial parasites ICT for malaria Workup for hemolysis: reticulocytes, LFTs, LDH, haptoglobin Workup for complications**
Treatment:	**Chloroquine resistant P. falciparum: artemisinin derivatives, quinine, tetracyclines, Chloroquine sensitive P. falciparum: chloroquine, hydroxychloroquine**

PARASITE CHARACTERISTICS:
- Blood-borne protozoa

TYPES OF PARASITES:
- Plasmodium vivax – benign tertian malaria
- P. ovale – benign tertian malaria
- P. malariae – benign quartan malaria
- P. falciparum – malignant tertian malaria
- P. knowlesi

TRANSMISSION:
- Bite of female Anopheles mosquito
- Transfusion malaria: caused by transfusion of blood from an infected donor.

RISK FACTORS:
- Living or travelling in endemic areas; extremes of age; immunosuppression; pregnant females

Table 3.20. CHARACTERISITCS OF DIFFERENT SPECIES OF MALARIA

	VIVAX	OVALE	MALARIAE	FALCIPARUM	KNOWLESI
Incubation period	8 – 17 days	10 – 17 days	18 – 40 days	8 – 11 days	9 – 12 days
Periodicity of symptoms	48 hours	48 hours	72 hours	36 – 48 hours	24 – 27 hours
Ability to form hypnozoites	Yes	Yes	No	No	No

PATHOGENESIS:
- Sporozoites injected into blood → enter hepatocytes and multiply to form merozoites → released in blood → enter erythrocytes → form schizonts → form merozoites which release by rupturing of RBC → merozoites enter new RBCs and cycle is repeated
- P. vivax and P. ovale produce dormant forms (called hypnozoites) which reside in liver and can recur later.
- In P. falciparum infection RBCs produce knobs which attach to endothelial cells as well as other RBCs → block capillaries and venules and sequester in organs (particularly brain)

PRESENTATION:

- Acute malaria:
  - Symptoms include headache, malaise, paroxysmal fever with shaking chills and sweating, cough, fatigue, malaise, shaking chills, arthralgias, myalgias, anorexia, lethargy, nausea, vomiting, diarrhea and jaundice.
  - On examination patients may have splenomegaly. Other findings include anemia, hepatomegaly, etc.
- Severe malaria (usually seen with falciparum malaria):
  - Cerebral malaria: altered level of consciousness, absence of signs of meningeal irritation, generalized convulsions
  - Metabolic manifestations: acidemia (acidotic/ labored deep breathing)
  - Severe anemia (massive intravascular hemolysis)
  - Hepatic manifestations: jaundice (indirect hyper-bilirubinemia due to hemolysis), liver failure
  - Pulmonary manifestations: Pulmonary edema (non-cardiogenic) or acute respiratory distress syndrome, rarely alveolar hemorrhages
  - Renal manifestations: hemoglobinuria (black-water fever), renal failure (pigment nephropathy)
  - Hypoglycemia
  - Coagulopathy or disseminated intravascular coagulation (DIC)
- Malaria in pregnancy:
  - It is associated with high rate of complications. These include low-birth weight, fetal distress, premature labour, still birth and increased mortality.
- Chronic malaria:
  - Tropical splenomegaly: chronic or repeated malaria infections lead to hypergammglobulinemia, normocytic anemia and splenomegaly (often massive). Patients complain of abdominal mass or left hypochondriac pain (dragging sensation or sharp pain).
  - Quartan malarial nephropathy: chronic or repeated malaria infections (especially P. malariae) lead to immune-complex injury to renal glomeruli and causes nephrotic syndrome.
  - Possible association with EBV and malaria co-infection and development of endemic Burkitt's lymphoma.
- Concomitant infections:
  - Concomitant infections with two different Plasmodium species, dengue virus and salmonella have been reported.

INVESTIGATIONS:

- CBC: anemia, thrombocytopenia
- Light microscopy of Giemsa stained blood smears every 6 to 12 hourly for 48 hours
- Rapid diagnostic tests
- Molecular diagnostic tests
- LFT's: raised indirect bilirubin
- Markers of hemolysis: haptoglobin, LDH, reticulocyte count
- G6PD: before prescribing primaquine

MANAGEMENT:

- Acute uncomplicated malaria:
  - Chloroquine-susceptible P. falciparum and other Plasmodium species
    - CHLOROQUINE 600 mg base (1000 mg salt) followed by 300 mg base (500 mg salt) at 6, 24 and 48 hours OR
    - HYDROXYCHLOROQUINE 620 mg base (800 mg salt) followed by 310 mg base (400 mg salt) at 6, 24 and 48 hours.
  - Chloroquine-resistant P. falciparum:
    - ARTEMETHER + LUMEFANTRINE 80/480 STAT then after 8 hours then twice daily for two days OR
    - ARTESUNATE 4 mg/kg + AMODIAQUINE 10 mg/kg once daily for three days OR
    - ARTESUNATE 4 mg/kg + MEFLOQUINE 25 mg base/kg for three days OR

        - ARTESUNATE 4 mg/kg for three days + SULFADOXINE-PYRIMETHAMINE 25/1.25 mg base/kg single dose OR
        - ATOVAQUONE 1000 mg + PROGUANIL 400 mg once daily for three days OR
        - DIHYDROARTEMISININ 120 mg + PIPERAQUINE 960 mg for three days OR
        - QUININE SULFATE 542 mg base (650 mg salt) thrice daily for 3 – 7 days + any of following
            - DOXYCYCLINE 100 mg twice daily for seven days
            - TETRACYCLINE 250 mg four times daily for seven days
            - CLINDAMYCIN 20 mg base/kg/day in three divided doses for 7 days
            - SULFADOXINE-PYRIMETHAMINE
        - OR MEFLOQUINE + ARTESUNATE
    - In case of P. ovale and P. vivax treatment should be given to eradicate hypnozoites.
        - PRIMAQUINE 30 mg (0.25 – 0.5 mg base/kg) daily for 14 days after ruling out G6PD deficiency. In case of mild G6PD deficiency use 45 mg (0.75 mg base/kg) once weekly for 8 weeks. In case of moderate to severe G6PD deficiency use CHLOROQUINE 150 mg base (500 mg salt) once weekly for 8 weeks.
    - In case of P. falciparum a single dose of PRIMAQUINE 0.25 mg/kg should be given to reduce transmission (except pregnant females and G6PD deficient)
- Complicated falciparum malaria
    - ARTESUNATE 2.4 mg/kg IV or IM at 0, 12 and 24 hours then once daily for 3 days. The treatment can be switched to oral therapy after 24 hours. If artesunate unavailable then WHO prefers ARTEMETHER over QUININE.
    - QUINIDINE 24 mg/kg diluted in 250 ml NS IV as infusion over 4 hours THEN after 8 hours start as 12 mg/kg iv infusion over 4 hours and repeat every 8 hourly for 3 – 7 days.
    - QUININE 648 mg orally thrice daily for 7 days.
- For pregnant females:
    - Uncomplicated P. falciparum malaria during first trimester: use QUININE + CLINDAMYCIN for 7 days.
    - CHLOROQUINE in anti-malarial doses is not linked with any problems.
    - PRIMAQUINE and TETRACYCLINS should not be used.
    - Relapse should be prevented by giving CHLOROQUINE once weekly till completion of pregnancy and breast-feeding.
- Chemoprophylaxis:
    - Travel to areas with high chloroquine resistance: mefloquine, doxycycline, malarone
    - Travel to areas with high chloroquine resistance: chloroquine, proguanil

Table 3.21. POOR PROGNOSTIC FEATURES IN SEVERE PLASMODIUM FALCIPARUM MALARIA

Clinical criteria:

- Marked agitation, hyperventilation, hypothermia, prostration, bleeding, deep coma, repeated convulsions, anuria, shock
- GCS <11

Laboratory criteria:

- RBS <2.2 mmol/L (<40 mg/dL)
- Lactate level >5 mmol/L
- Arterial pH <7.3, serum bicarbonate <15 mmol/L
- Serum creatinine >265 µmol/L (>3 mg/dL) or blood urea >20 mmol/L
- Total bilirubin >50 µmol/L (>3 mg/dL)
- Raised AST or ALT (greater than three times upper limit normal)
- Elevated muscle enzymes (raised CPK or myoglobin)
- Elevated urate level >600 µmol/L
- White cell count >12,000/ µL
- Severe anemia (PCV <15% or hemoglobin ≤5 g/dL)
- Coagulopathy (platelets <50,000/ µL, PT >3s of control, prolonged APTT, fibrinogen <200 mg/dL)
- Hyper-parasitemia (parasites >100,000/µL, >20% parasites in pigmented trophozoite or schizont form, >5% of neutrophils with visible pigment)
- Shock

⇨ ***Recrudescence is the return of malaria within days to weeks after treatment. It is due to survival of parasites in blood due to ineffective treatment or immunosuppression.***

⇨ ***Relapse is the return of malaria within weeks to months after treatment. It is due to release of new hypnozoites.***

⇨ ***Plasmodium falciparum is the most malignant Plasmodium species.***

3.7.2. AMEBIASIS

CAUSATIVE ORGANISM:

- Entameba histolytica

PATHOPHYSIOLOGY:

- Cysts in contaminated food or water are ingested → trophozoites emerge in small intestine → pass to colon → multiply and cause inflammation and ulceration → colitis

PRESENTATION:

- Dysentery: small quantity, frequent soft stools containing mucus, often with tenesmus, abdominal pain and occasionally bloody.
- Liver abscess
- Abscesses elsewhere
- Other symptoms include headache, nausea, anorexia

INVESTIGATIONS:

- Fresh stool microscopy: shows trophozoites ontaining RBCs
- Sigmoidoscopy: shows flask-shaped ulcers
- Fluorescent antibody

MANAGEMENT:

- Metronidazole
- Diloxanide furoate

3.7.3. GIARDIASIS

CAUSATIVE ORGANISM:

- Giardia intestinalis (G. lamblia)

PATHOPHYSIOLOGY:

- Cysts ingested → attaches to duodenal and jejunal mucosa → inflammation → leads to malabsorption

PRESENTATION:

- Watery diarrhea
- Anorexia, nausea, abdominal distension
- Malabsorption

INVESTIGATIONS:

- Stool microscopy for cysts and trophozoites

MANAGEMENT:

- Metronidazole
- Tinidazole

3.7.4. LEISHMANIASIS

"It is an infection of reticulo-endothelial system caused by Leishmania species."

QUICK FACTS: LEISHMANIASIS	
Pathology:	**Flagellates acquired after sandfly bite → infect macrophages → release amastigotes → invade skin, liver, spleen or bone marrow**
Presentation:	**Visceral: fever, weight loss, hepatosplenomegaly, pancytopenia, night sweats, weakness, skin hyperpigmentation** **Cutaneous: painless erythematous papule on skin → changes to plaque or ulcer → heals** **Mucocutaneous: cutaneous ulcers followed by mucosal surface ulcers**
Diagnosis:	**Peripheral smear: amastigotes in monocytes and neutrophils** **Blood, bone marrow, liver and splenic aspirates** **Antibody to K39**
Treatment:	**Pentavalent antimony compounds, amphotericin, miltefosine, pentamidine, dapsone**

PROTOZOAN CHARACTERISTICS:

- Leishmania species

TRANSMISSION:

- Bite of female sandfly (Phlebotomus species in East and Lutzomyia in West)

RISK FACTORS:

- Poverty, malnutrition, migration, deforestation, HIV infection

PATHOGENESIS:

- Flagellates are injected into the humans after sandfly bite → enter macrophages → change to amastigote form → multiply and release by rupturing cell → attack fresh cells and cycle is repeated → depending on host immune response, parasites may also invade skin, liver, spleen or bone marrow through macrophages.

PRESENTATION:

- Viseral (kala-azar/ black fever/ Dumdum fever/ Assam fever):
  - Fever, wiehgt loss, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia.
  - Other features may include night sweats, weakness, diarrhea and anorexia.
  - There is characteristic skin hyperpigmentation.
- Cutaneous (most common form): bite on exposed parts → incubates over weeks to months → formation of painless erythematous papule → forms plaque or ulcer → heals spontaneously in months
  - Localized: single lesion (new world species) to multiple lesions (old world species).
  - Diffuse: generalized lesions start after primary lesion due to defective cell-mediated immunity. It can recur after treatment.
  - Post-kala-azar dermal leishmaniasis: following treatment multiple macules form which transform into plaques and nodules and involve face and trunk.
- Mucocutaneous (espundia): following cutaneous lesions, ulcers appear in nose, mouth, oropharynx and trachea which may lead to destruction of these structures.

INVESTIGATIONS:

- CBC: shows pancytopenia
- Peripheral smear: amastigotes in monocytes and neutrophils
- Skin biopsy, mucosal granuloma biopsy or dental scrapings in case of cutaneous or mucocutaneous leishmaniasis
- Blood, bone marrow, liver and splenic aspirates in visceral disease: amastigotes on plain examination and promastigotes on culture (NNN medium, Schneider drosophila medium)

- Serological tests (antibodies to recombinant K39 antigen)

MANAGEMENT:
- Pentavalent antimony compounds e.g. sodium stibogluconate, meglumine antimonate
- Amphotericin B
- Oral miltefosine
- Intramuscular pentamidine
- Oral dapsone, ketoconazole, fluconazole

3.7.5. TRYPANOSOMIASIS

"Trypanosomiasis is an infection caused by Trypanosoma species."

3.7.5.1. AFRICAN TRYPANOSOMIASIS

CAUSATIVE ORGANISM:
- Trypanosoma brucei.

TRANSMISSION:
- Bite of infected tsetse fly (Glossina)

PRESENTATION:
- Early/ hemolymphatic stage: fever, rashes, lymphadenopathy
- Late/ neurologic stage: headaches, daytime somnolence, nighttime insomnia, CNS manifestations

INVESTIGATIONS:
- Blood smear, aspirates from chancre, lymph node or bone marrow and CSF may reveal trypanosomes

MANAGEMENT:
- See table 3.22.

Table 3.22. TREATMENT OF TRYPANOSOMIASIS

	STAGE 1	STAGE 2
EAST AFRICAN VARIANT	Suramin	Melarsoprol
WEST AFRICAN VARIANT	Pentamidine isethionate or Suramin	Melarsoprol or Eflornithine

3.7.5.2. AMERICAN TRYPANOSOMIASIS

CAUSATIVE ORGANISMS:
- It is caused by Trypanosoma cruzi.

TRANSMISSION:
- Bite of a reduvid or triatomine bug

PATHOPHYSIOLOGY:
- Local inflammation at bite site → carried to regional lymph nodes →ingested by inflammatory cells → forms amastigotes → multiply → form trypomastigotes → invade blood stream → infect reticulo-endothelial cells, muscles, nerves → cardiomyopathy (myocardial necrosis, inflammation and ganglion cell destruction), esophageal and colonic dilatation (destruction of autonomic nervous system)

PRESENTATION:
1. Early phase:
    a. Usually asymptomatic
    b. Bug-bite → local red nodule (chagoma)
2. Acute phase:

   a. flu-like illness, myalgias, malaise, lymphadenopathy, splenomegaly
3. Chronic phase:
   a. Congestive heart failure (right sided heart failure more common), cardiac aneurysms.
   b. Neurological dysfunction in GI tract leading to megaesophagus, megacolon, etc.

INVESTIGATIONS:

- Acute phase:
  - Blood smear reveals parasites.
  - Blood cultures on special media
- Chronic phase:
  - Xenodiagnoses
  - Serological tests

MANAGEMENT:

- Acute phase:
  - NIFURTIMOX or BENZNIDAZOLE
- Chronic phase:
  - Consider BENZNIDAZOLE
  - Supportive therapy
    - Anti-arrhythmics, anti-coagulants,
    - Manage heart failure
    - Esophageal disease: soft diet, nifedipine or sublingual nitrates before meals, esophageal dilatation, surgery
    - Colonic disease: high-fiber diet, increased fluids, laxatives, surgery

3.7.6. TOXOPLASMOSIS

"Toxoplasmosis is caused by intracellular parasite Toxoplasma gondii."

QUICK FACTS: TOXOPLASMOSIS	
Pathology:	**Ingestion of cysts → toxoplasma infection**
Presentation:	**Immunocompetent: subclinical** **Immunocompromised: encephalopathy, meningoencephalitis, mass lesions in brain** **Congenital: chorioretinitis**
Diagnosis:	**IgM and IgG** **Fundoscopy**
Treatment:	**Immunocompetent: no treatment** **Immunocompromised: pyrimethamine-sulfadiazine, trimethoprim-sulfamethoxazole, dapsone**

CAUSATIVE ORGANISM:

- Toxoplasma gondii

TRANSMISSION:

- Ingestion of tissue cysts from contaminated soil or food
- Trans-placental transmission (highest risk during third trimester)

PATHOPHYSIOLOGY:

- Infection is subclinical and life-long in immno-competent individuals. In case of immuno-suppression, infection gets reactivated.

PRESENTATION:

- Immuno-competent patients:
  - Usually asymptomatic, cervical lymphadenopathy (most common finding), generalized lymphadenopathy, fever, headache, malaise, fatigue.

- Immuno-compromised patients:
    - It is mostly due to re-activation of latent infection.
    - It presents with encephalopathy, meningo-encephalitis and mass lesions in brain (particularly brain-stem, basal ganglia, pituitary gland and corticomedullary junction).
- Congenital infection:
    - Initially asymptomatic but can reactivate to form clinical disease e.g. chorioretinitis.

INVESTIGATIONS:
- Serological tests e.g. IgM and IgG
- Ophthalmological examination

MANAGEMENT:
- Immuno-competent patients: no treatment
- Immuno-compromised patients: PYRIMETHAMINE + SULFADIAZINE or TRIMETHOPRIM + SULFAMETHOXAZOLE or DAPSONE.
- Congenital infection: one year PYRIMETHAMINE, SULFADIAZINE and FOLINIC ACID.
- Ocular toxoplasmosis: PYRIMETHAMINE and either SULFADIAZINE or CLINDAMYCIN.

3.7.7. BABESIOSIS

"It is caused by Babesia microti."

CAUSATIVE AGENT:
- Babesia microti and other species

TRANSMISSION:
- Bite of deer tick (Ixodes)

PATHOPHYSIOLOGY:
- sporozoites enter body following tick bite → intra-erythrocytic infection → multiply to form merozoites → release by rupturing RBCs

PRESENTATION:
- fever, chills, sweats, myalgias, arthralgias, fatigue

INVESTIGATIONS:
- Giemsa-stained thin smears, serological tests

TREATMENT:
- For mild disease: ATOVAQUONE + AZITHROMYCIN, CLINDAMYCIN + QUININE
- For severe disease: CLINDAMYCIN + QUININE

3.8. HELMINTHIC INFECTIONS (NEMATODES)

3.8.1. TRICHINELLOSIS

CAUSATIVE ORGANISMS:
- Trichinella species (notably T. spiralis).

TRANSMISSION:
- Ingestion of uncooked meat (usually pork)

PATHOPHYSIOLOGY:
- Encysted larvae in meat → invade small bowel mucosa →cause abdominal symptoms → migrate via blood to muscles (particularly extraocular muscles, biceps, etc.)

PRESENTATION:
- First week of infection: gastrointestinal symptoms
- Second week of infection: hypersensitivity reaction with eosinophilia, peri-orbital and facial edema, myocarditis, arrhythmias.
- Third week of infection: myositis, myalgias, muscle edema.

INVESTIGATIONS:
- CBC: marked eosinophilia; Trichinella-specific antibodies; Microscopic examination of fresh muscle tissue

MANAGEMENT:
- MEBENDAZOLE or ALBENDAZOLE; glucocorticoids for myocarditis and myositis

3.8.2. ASCARIASIS

CAUSATIVE ORGANISM:
- Ascaris lumbricoides.

TRANSMISSION:
- Feco-oral transmission: ingestion of soil contaminated with infected feces

PATHOPHYSIOLOGY:
- Ingestion of eggs → hatch in intestine → invade mucosa → migrate to lungs → migrate through lung tissue → ascend via bronchi → swallowed → mature in intestine and lay eggs

PRESENTATION:
- Cough, sub-sternal discomfort, dyspnea, eosinophilia, asthma-like presentation; Eosinophilic pneumonitis (Loffler's pneumonia); Abdominal pain, small bowel obstruction, biliary obstruction, pancreatitis

INVESTIGATIONS:
- Stool D/R shows ascaris eggs and occasionally adult worms

MANAGEMENT:
- ALBENDAZOLE 400 mg single dose
- MEBENDAZOLE 500 mg single dose
- IVERMECTIN 150 – 200 µg/kg single dose
- PYRANTEL PAMOATE 11 mg/kg (up to 1 g) single dose

3.8.3. HOOKWORM INFESTATION

CAUSATIVE ORGANISMS:
- Ancylostoma duodenale (old world hookworm), Necator americanus (new world hookworm).

TRANSMISSION:
- direct penetration of skin by larvae in fecally contaminated soil

PATHOPHYSIOLOGY:
- Larvae penetrate skin → reach lungs via blood → invade alveoli → ascend up the bronchi → swallowed → mature in small intestine → attach to mucosa and suck blood

PRESENTATION:

- Asymptomatic; asthma like presentation; iron deficiency anemia; hypoproteinemia; malabsorption; ground-itch (pruritic rash at the site of skin penetration)

INVESTIGATIONS:
- Stool D/R for hookworm eggs

MANAGEMENT:
- Antihelminthics (as ascariasis)
- Iron replacement

3.8.4. STRONGYLOIDIASIS

CAUSATIVE ORGANISM:
- Strongyloides stercoralis

TRANSMISSION:
- Direct penetration of skin or mucosa by filariform larva in fecally contaminated soil

PATHOPHYSIOLOGY:
- Larvae spread via blood → reach lungs → invade alveoli → ascend up bronchi → swallowed → mature in small intestine → penetrate mucosa and lay eggs which hatch there

PRESENTATION:
- Recurrent urticarial; larva currens (pruritic erythematous eruption caused by larval migration); bdominal symptoms; weight loss

INVESTIGATIONS:
- Stool D/R for rhabditiform larvae; Anti-strongyloides antibodies (ELISA)

MANAGEMENT:
- IVERMECTIN 200 µg/kg daily for two days (longer course for disseminated disease) or ALBENDAZOLE 400 mg daily for 3 days

3.8.5. ENTEROBIASIS

CAUSATIVE ORGANISM:
- Enterobius vermicularis (pinworm)

TRANSMISSION:
- Direct transmission of eggs from peri-anal scratching to mouth or indirectly via clothes or furniture

PATHOPHYSIOLOGY:
- Worms reside in ileocecal region → female worms migrate to anal region to lay eggs → eggs hatch into larvae → migrate upwards into intestine

PRESENTATION:
- Primarily occurs in children; peri-anal pruritis (usually worse at night)

INVESTIGATIONS:
- Microscopic examination of cellulose acetate tape applied to peri-anal region in morning

MANAGEMENT:
- MEBENDAZOLE, ALBENDAZOLE or PYRANTEL PAMOATE

3.8.6. LYMPHATIC FILARIASIS

"It is an infection of lymphatics and lymph nodes caused by lymphatic filarias."

CAUSATIVE ORGANISMS:
- Wuchereria bancrofti (most common), Brugia malayi, B. timori

PATHOPHYSIOLOGY:
- lymphangitis and lymphadenitis → chronic lymphatic obstruction and elephantiasis

PRESENTATION:
- fever, inguinal or axillary lymphadenopathy, limb or genital swelling

INVESTIGATIONS:
- detection of microfilariae in blood,

MANAGEMENT:
- DIETHYLCARBAMZINE (DEC), ALBENDAZOLE, DEC + ALBENDAZOLE, DOXYCYCLINE

3.8.7. ONCHOCERCIASIS

River blindness

"It is an infection caused by Onchocerca species."

CAUSATIVE ORGANISM:
- Onchocerca volvulus

TRANSMISSION:
- bite of infected blackfly

PATHOPHYSIOLOGY:
- skin nodules

PRESENTATION:
- pruritic rash, onchocercomata (), ocular inflammation and lesions leading to blindness

INVESTIGATIONS:
- examination of excised nodule or skin snip, serology

MANAGEMENT:
- IVERMECTIN, DOXYCYCLINE

3.9. HELMINTHIC INFECTIONS (TREMATODES)

3.9.3. SCHISTOSOMIASIS

CAUSATIVE ORGANISMS:
- Schistosoma mansoni
- S. japonicum
- S. mekongi
- S. intercalatum
- S. hematobium

TRANSMISSION:
- Direct penetration of skin by cercariae

PATHOPHYSIOLOGY:
- Cercariae penetrate skin → form schistosomula → migrate through veins or lymphatics → reach lungs → reach liver → sexually mature forms migrate to final destination to lay eggs (venous plexus of urinary bladder and ureters in case S. hematobium and mesentery in case of others).

PRESENTATION:
- Swimmer's itch: pruritic maculopapular rash at cercarial infection site
- Acute schistosomiasis (Katayama fever): fever, generalized lymphadenopathy, hepatosplenomegaly, significant eosinophilia
- Chronic schistosomiasis:
    - Intestinal manifestations: abdominal pain, bloody diarrhea, portal hypertension, varices, hepato-splenomegaly
    - Urinary manifestations: dysuria, hematuria, obstructive uropathy, granulomatous cystitis, increased risk of squamous cell carcinoma bladder
    - Pulmonary manifestations: endarteritis obliterans, pulmonary hypertension, cor pulmonale
    - CNS disease: Jacksonian epilepsy, transverse myelitis

INVESTIGATIONS:
- Stool D/R for eggs
- Serological tests
- Rectal biopsy

MANAGEMENT:

- Glucocorticoids during acute phase
- PRAZIQUANTEL for one day

3.9.3. LIVER FLUKES

- Clonorchis sinensis, Opisthorchis viverrin and O. felineus cause cholangitis, cholangiohepatitis and biliary obstruction and are associated with cholangiocarcinoma.

Fasciola hepatica and gigantica cause hepatitis, biliary obstruction and biliary cirrhosis.

3.9.3. LUNG FLUKES

- Paragonimus species causes alveolar hemorrhages, pulmonary infiltrates with eosinophilia, bronchitis and CNS disease.

3.10. HELMINTHIC INFECTIONS (CESTODES)

3.10.1. TAENIASIS

CAUSATIVE ORGANISMS:

- Taenia saginata (beef tapeworm), Taenia asiatica (swine tapeworm), Taenia solium (pork tapeworm)

TRANSMISSION AND PATHOGENESIS:

- Humans are definitive hosts.
- Eggs are excreted in faeces → ingested by cattle or pigs → larvae encyst in skeletal muscles → if humans eat raw or undercooked meat, cysticerci mature and attach in small intestine

PRESENTATION:

- Proglottids in stools, perianal discomfort, abdominal pain, nausea, anorexia, weight loss.

INVESTIGATIONS:

- Stool examination reveals eggs or proglottids
- Cellophane test: applying a cellophane-tape in the perianal area may reveal eggs.
- CBC may show eosinophilia
- IgE levels may be raised.

MANAGEMENT:

- PRAZIQUANTEL 10 mg/kg single dose

3.10.2. CYSTICERCOSIS

CAUSATIVE ORGANISM:

- Taenia solium

TRANSMISSION:

- Ingestion of eggs of Taenia solium (unlike taeniasis solium where larvae are ingested in uncooked meat)

PATHOPHYSIOLOGY:

- Eggs ingested → hatch into larvae in intestine → penetrate intestinal wall → reach skeletal muscles, brain, eye and subcutaneous tissue and form cysticerci → in brain, survive immune responses → eventually degenerate → surrounding inflammation causes manifestations of disease

PRESENTATION:

- Seizures, hydrocephalus, mass lesions, raised ICP

INVESTIGATIONS:

- Stool D/R, neuroimaging

MANAGEMENT:

- Intestinal infection:
  - PRAZIQUANTEL (single dose)
- Neurocysticercosis:
  - ALBENDAZOLE 15 mg/kg/day for 8 – 28 days or PRAZIQUANTEL 50 – 100 mg/kg/day in three divided doses for 15 – 30 days
  - High-dose glucocorticoids

- CIMETIDINE (to inhibit praziquantel metabolism induced by glucocorticoids)
- Anti-epileptics
- Treatment of hydrocephalus

⇨ ***Larval stage occurs in pigs in case of taeniasis whereas this stage occurs in humans in case of cysticercosis (accidental infection).***

3.10.3. ECHINOCOCCOSIS

Aka hydatidosis

CAUSATIVE ORGANISM:
- Echinococcus granulosus (cystic echinococcosis), Echinococcus multilocularis (alveolar echinococcosis)

TRANSMISSION:
- ingestion of eggs passed in feces of dogs by humans (E. granulosus)

PATHOPHYSIOLOGY:
- Larval cysts develop in many organs including liver (most common), liver, etc.

PRESENTATION:
- Cysts present as space-occupying lesions in different organs

INVESTIGATIONS:
- Ultrasound, CT scan, serological tests

MANAGEMENT:
- MEBENDAZOLE or ALBENDAZOLE
- PAIR (percutaneous aspiration, injection of scolicidal agents, and reaspiration) for uncomplicated lesions
- Surgical removal

3.10.4. DIPHYLLOBOTHRIASIS

Aka fish tape-worm infestation

CAUSATIVE ORGANISM:
- Diphyllobothrium species esp. D. latum (Fish tape-worm)

TRANSMISSION:
- Ingestion of infected raw or smoked fish

PATHOGENESIS:
- Attaches to ileal and jejunal mucosa → decreases vitamin B12 absorption.

PRESENTATION:
- Asymptomatic; passage of proglottids in stools; dyspepsia; megaloblastic anemia

MANAGEMENT:
- Drug of choice: PRAZIQUANTEL 5 – 10 mg/kg once
- Alternative treatment: NICLOSAMIDE
- Surgery in case of intestinal obstruction.
- VITAMIN B12 replacement.

3.11. ARTHROPOD RELATED DISEASES

3.11.1. INSECTS

- Lice:
  - Cause pediculosis capitis, pediculosis corporis, pediculosis pubis
- Fleas
  - Xenopsylla cheopis spreads plague
- Bugs
  - Bed-bugs
  - Reduviid bugs: spread trypanosomiasis
- Flies
  - Chrysops (deer flies): spread loiasis
  - Similum (black flies): spread onchocerciasis
  - Tsetse flies spread African trypanosomiasis
  - Sandfly spreads leishmaniasis
  - Different flies: cause myaisis
- Mosquitoes
  - Anopheles: spread malaria
  - Culex: spread filariasis
  - Aedes: spread dengue, yellow fever, chikungunya, zikavirus, West Nile fever, Brugia species, filariasis
  - Mansonia: spread Rift valley fever virus

3.11.2. ARACHNIDS

- Ticks: spread lyme disease, African tick bite fever, rocky mountain spotted fever, etc.
- Mites: cause scabies and spread scrub typhus, rickettsial pox, etc.
- Spiders: bites cause local pain and necrosis, muscle spasms and hemolysis.
- Scorpions: bites cause local pain and systemic symptoms

3.11.3. CRUSTACEANS

- These include cyclops, cray fishes, fresh water crabs, lobsters and shrimps.

3.11.4. MYRIAPODS

- Include centipedes.

3.12. FUNGAL INFECTIONS

3.12.1. CANDIDIASIS

QUICK FACTS: CANDIDIASIS	
Pathology:	**Immunocompromised state → infections**
Presentation:	**Oral thrush** **Esophageal candidiasis (AIDS defining)** **Laryngitis, tracheobronchitis, pneumonia (AIDS defining)** **Vulvovaginitis** **Disseminated candidiasis**
Diagnosis:	**Pseudohyphae or hyphae in samples**
Treatment:	**Antifungals**

CAUSATIVE AGENTS:

- Candida species (C. albicans, C. krusei, C. tropicalis, C. glabrata, C. Parapsilosis, C. auris)

RISK FACTORS:

- Immunocompromised status, diabetes mellitus, HIV/AIDS, use of dentures, patients with indwelling catheters, hospitalized patients, intravenous drug abuse, splenectomy.

PRESENTATIONS:

- Mucocutaneous candidiasis:
  - Oropharyngeal candidiasis/ thrush: white, painless, confluent patches in mouth or on tongue
  - Gastrointestinal candidiasis: usually occurs in esophagus. It is an AIDS defining illness.
  - Respiratory candidiasis:
    - These include laryngitis, tracheobronchitis and pneumonia.
    - These are AIDS-defining illnesses.
  - Vulvovaginal candidiasis: pruritis, pain and vaginal discharge containing white curds
  - Other genitourinary candidiasis: balanitis, cystitis, ascending pyelonephritis
  - Inter-trigo: intertriginous dermatitis (between folds of skin) is frequently colonized by Candida.
  - Chronic mucocutaneous candidiasis: chronic infection of hairs, nails, skin and mucosal surfaces which is poorly responsive to anti-fungals because of defective immune system. It is associated with endocrinopathies like hypoparathyroidism, Addison's disease, hypothyroidism, diabetes mellitus and polyglandular syndromes.
- Systemic candidiasis: occurs by dissemination through blood-stream
  - Candidemia: suspected by fever unresponsive to broad-spectrum antibiotics in a patient with multiple risk factors. It may cause endocarditis.
  - Disseminated candidiasis: causes deep organ infections e.g. pneumonia, multiple lung abscesses, renal infection, meningitis, etc.

INVESTIGATIONS:

- Pseudohyphae or hyphae in appropriate samples from a suspected patient are diagnostic.
- Simple isolation from catheters represents colonization rather than infection.
- B-glucan test: rules out the infection in case of suspected disseminated disease.

MANAGEMENT:

- Mucocutaneous candidiasis:
  - Oropharyngeal candidiasis: Topical NYSTATIN, CLOTRIMAZOLE, ECONAZOLE, MICONAZOLE or KETOCONAZOLE
  - Vulvovaginal infections: daily topical agents or FLUCONAZOLE 150 mg single dose
  - Esophageal or tracheobronchial infections: FLUCONAZOLE or ITRACONAZOLE daily for 2 – 3 weeks.

- Longer treatment is needed in HIV-positive patients.
- Higher doses are given in case of invasive disease.

- Candidemia:
  - Without neutropenia: FLUCONAZOLE
  - With neutropenia: AMPHOTERICIN B (lipid formulations better than conventional in terms of side-effects), echinocandins, high dose FLUCONAZOLE or VORICONAZOLE

⇨ ***Candidiasis is the most important fungal nosocomial infection.***

3.12.2. ASPREGILLOSIS

QUICK FACTS: ASPERGILLOSIS	
Pathology:	**Infection in immunocompromised patients**
Presentation:	**Invasive pulmonary aspergillosis; Invasive sinusitis; Disseminated aspergillosis Chronic pulmonary aspergillosis: to brain, skin, thyroid, bone Aspergilloma: fungal balls in residual lung cavities Allergic bronchopulmonary aspergillosis: asthma like syndrome due to IgE-mediated hypersensitivity**
Diagnosis:	**Cultures, HRCT, histopathology**
Treatment:	**Anti-fungals e.g. voriconazole, itraconazole; Surgery for aspegilloma**

CAUSATIVE ORGANISM AND TRANSMISSION:

- A. fumigatus (most cases), other Aspergillus species
- Transmitted by inhalation

RISK FACTORS:

- Immuno-compromised patients (neutropenia, glucocorticoid use, leukemia, post-hematopoietic stem-cell transplant recipients)

PRESENTATION:

- Invasive pulmonary aspergillosis:
  - Presents (acutely or subacutely)as fever, cough, chest discomfort, hemoptysis or dyspnea.
- Invasive sinusitis:
  - Presents as fever, nasal or facial discomfort and nasal discharge.
- Disseminated aspergillosis:
  - Disseminates to other organs like brain, skin, thyroid, bone, etc.
- Chronic pulmonary aspergillosis:
  - Presents as single or multiple slowly enlarging cavities with pericavity infiltrates with pulmonary symptoms.
- Aspergilloma:
  - These are fungal balls forming in residual cavities (mostly tubercuolous) and can present as hemoptysis.
- Allergic bronchopulmonary aspergillosis (ABPA):
  - It is an IgE-mediated hypersensitivity reaction towards Aspergillus and presents as an asthma-mimic.

INVESTIGATIONS:

- Cultures
- Galactomannan antigen testing
- Histopathology
- High-resolution CT scan: halo sign

MANAGEMENT:

- Anti-fungals e.g. ITRACONAZOLE, VORICONAZOLE
- Surgical treatment for aspergillomas

3.12.3. CRYPTOCOCCOSIS

CAUSATIVE ORGANISM:
- Encapsulated yeast C. neoformans

TRANSMISSION:
- Via inhalation of pigeon droppings contaminating soil

RISK FACTORS:
- Immuno-compromised status (AIDS, post-transplant patients)

PATHOPHYSIOLOGY:
- Spores are inhaled into alveoli → ingested by macrophages → survive phagocytosis due to capsule →disseminate → organ damage occurs due to fungal burden as there is little inflammation

PRESENTATION:
- CNS disease: sub-acute or chronic meningoencephalitis
- Pulmonary disease: cough, dyspnea, pleuritic pain
- Skin lesions

INVESTIGATIONS:
- Blood: fungal cultures, cryptococcal antigen test
- CSF: India ink smear, fungal culture, cryptococcal antigen test

MANAGEMENT:
- Anti-fungals in case of CNS disease: AMPHOTERICIN B ± FLUCYTOSINE for 2 weeks followed by FLUCONAZOLE for 8 – 10 weeks. Pulmonary disease may not need treatment

3.12.4. MUCORMYCOSIS

CAUSATIVE ORGANISMS:
- Rhizopus species (most common), Mucor species

CHARACTERISTICS:
- Thick-walled aseptate hyphae that branch at right angles

TRANSMISSION:
- Inhalation of conidia or ingestion or direct inoculation by trauma

RISK FACTORS:
- Diabetes, diabetic ketoacidosis, neutropenia, chronic steroid use, desferoxamine therapy

PATHOPHYSIOLOGY:
- Inhalation of conidia → form hyphae → invade blood vessels → infarction, necrosis and thrombosis of tissues → life-threatening

PRESENTATION:
- Rhinocerebral disease:
  - It starts as unilateral retro-orbital headache, facial pain, numbness, fever, hyposmia, nasal stuffiness, nasal discharge (epistaxis or black discharge).
  - It invades neighboring structures giving rise to diplopia, vision loss, orbital swelling, facial cellulitis, necrotic eschars, ophthalmoplegia, proptosis and ptosis.
  - CNS involvement leads to coma.
- Pulmonary disease: pulmonary symptoms

- Cutaneous disease: cellulitis with dermal necrosis and black eschar.
- Gastrointestinal disease
- Disseminated disease involves multiple organs.
- Others e.g. CNS disease

INVESTIGATIONS:
- Rhinocerebral disease: CT scan or MRI of paranasal sinuses, nasal endoscopy with biopsy of lesions
- Pulmonary disease: broncho-alveolar lavage

MANAGEMENT:
- AMPHOTERICIN B DEOXYCHOLATE or LIPOSOMAL form
- DESFERASIROX (iron chelator)
- Correct risk factors.

3.12.5. HISTOPLASMOSIS

CAUSATIVE ORGANISM:
- Histoplasma capsulatum

CHARACTERISTICS:
- Dimorphic fungus

TRANSMISSION:
- Inhalation of microconidia

PATHOPHYSIOLOGY:
- Inhalation of microconidia → reach alveoli → form yeasts → granulomatous inflammation

PRESENTATION:
- Immunocompetent patients: flu-like illness followed by hilar or mediastinal lymphadenopathy
- Immunocompromised patients:
- Acute course: widespread lung infiltrates, shock, multi-organ failure
- Sub-acute course: fever, hepato-splenomegaly, weight loss.

INVESTIGATIONS:
- Fungal cultures
- Histoplasma antigen assay

MANAGEMENT:
- Anti-fungals e.g. AMPHOTERICIN B, ITRACONAZOLE

3.12.6. COCCIDIOIDOMYCOSIS

- It is a pulmonary infection with erythema nodosum and joint pains caused by C. immitis or C. posadasii. Disease may disseminate to other organs e.g. bone, skin, joint, meninges, etc. It is diagnosed by means of serology and cultures. Treatment is AMPHOTERICIN B, FLUCONAZOLE OR ITRACONAZOLE.

3.12.7. BLASTOMYCOSIS

- It is a pulmonary infection caused by Blastomyces dermatitidis. It can have cutaneous, skeletal or CNS manifestations especially in immuno-compromised patients. It is diagnosed by smears or cultures of sputum, pus or tissue or antigen detection in serum or urine. Treatment is AMPHOTERICIN B, ITRACONAZOLE or FLUCONAZOLE.

3.12.8. SPOROTRICHOSIS

- It is a lymphocutaneous, osteoarticular and pulmonary infection caused by Sporothrix schenkii. It is transmitted by inoculation into tissues by thorn-pricks in gardens. It is diagnosed by culture of exudate or skin biopsy. Treatment is ITRACONAZOLE.

9. IMMUNOLOGY AND RHEUMATOLOGY

9.1. HYPERSENSITIVITY/ALLERGY REACTIONS

"Hypersensitivity/allergy is a phenomenon in which an immune reaction results in an exaggerated response harmful for the host."

Table 9.1: MODIFIED GELL AND COOMB'S CLASSIFICATION OF HYPERSENSITIVITY REACTIONS	
Types of hypersensitivity reactions	**Features with examples**
Type I hypersensitivity (Immediate/anaphylactic)	Foreign antigen react with IgE bound to mast cells → mast cells degranulate and release mediators like histamine, arachidonic acid metabolites and cytokines. Examples: Asthma, hay fever, eczema, allergic gastroenteropathy, atopy, anaphylaxis
Type II (cytotoxic) Now known as type IIa	IgM or IgG antibodies react with cell-bound antigens → activation of complement cascade → cell destruction. Examples: Immune hemolytic anemia, Rh hemolytic disease in newborn, Goodpasture's syndrome
Type III (immune-complex)	IgM or IgG antibodies bind to antigen → antigen-antibody complexes → deposit in different tissues → activate complement cascade → tissue injury Examples: Serum sickness, sub-acute bacterial endocarditis, hepatitis B, post-streptococcal GN, rheumatoid arthritis, SLE
Type IV (cell-mediated/delayed)	Activated T cells react against antigens IV-a: CD4+ Th1 lymphocyte activation leads to macrophage activation Examples: granuloma, type-1 diabetes IV-b: CD+Th2 activation with eosinophilic involvement Examples: persistent asthma, allergic rhinitis IV-c: cytotoxic CD8+Tlymphocyte activation with perforin-granzyme B mediated apoptosis Examples: SJS/ TENS IV-d: T lymphocytes lead to neutrophilic activation Examples: pustular psoriasis, acute generalized exanthematous pustulosis
Type V (antibody mediated cell stimulation) Now known as type IIb	Antibody binds to cell surface receptors and leads to over-function of that receptor Examples: Graves disease, autoimmune chronic idiopathic urticaria

9.2. ANAPHYLAXIS

"Anaphylaxis is a life-threatening multi-organ type 1 hypersensitivity reaction caused by release of chemokines from mast cells and basophils by IgE-dependent mechanisms."
*"**Anaphylactoid** is a clinically indistinguishable reaction in which release of chemokines from mast cells and basophils occurs by IgE-independent mechanisms."*

QUICK FACTS: ANAPHYLAXIS	
Pathology:	**Antigens combine with IgE bound to mast cells and basophils → degranulation and release of mediators**
Presentation:	**Dermatologic: flushing, urticarial, angioedema, pruritis, conjunctival injection** **Respiratory: nasal congestion, coryza, rhinorrhea, sneezing, wheezing, dyspnea** **Cardiovascular, gastrointestinal, neurologic and miscellaneous features**
Diagnosis:	**Clinical diagnosis**
Treatment:	**Stabilize** **Epinephrine 1:1000 IM or SC** **Inhaled beta-2 agonists, H1 and H2 receptor antaagonists, steroids**

Diagnosis requires any one of the following:

1. Acute onset illness with involvement of skin/ mucosa with either respiratory compromise, hypotension or end-organ dysfunction.

2. Two or more of following:
    a. Involvement of skin and/or mucosa
    b. Signs of respiratory compromise
    c. Falling blood-pressure or end-organ dysfunction
    d. Persistent gastrointestinal symptoms
3. Falling blood pressure within minutes to hours following exposure to a known allergen.

PATHOPHYSIOLOGY:

- Antigens bind to mast cells and basophils through IgE-IgE receptor complex. This leads to cellular activation and release of chemical mediators which lead to widespread effects in body. The mediators include **histamine (principal mediator)**, prostaglandins, leukotrienes (C4, D4 and E4 = slow-reacting substance of anaphylaxis/ SRS-A), acid hydrolases, neutral proteases, proteoglycans and interleukins. These lead to vasodilation, increased vascular permeability, smooth muscle contraction, and chemotaxis.
- Almost any substance can trigger anaphylaxis reaction however certain foods like peanuts, legumes, shellfish, milk, vaccines, insect stings, latex, beta-lactam antibiotics, aspirin, NSAIDs or exercise are commonly implicated. Anaphylactoid commonly occurs due to radiographic contrast material.

SYMPTOMS:

- **Dermatologic:** Flushing, urticaria, angioedema, cutaneous and/or conjunctival injection or pruritis, warmth, and swelling.
- **Respiratory:** nasal congestion, coryza, rhinorrhea, sneezing, throat tightness, wheezing, shortness of breath, cough, hoarseness, dyspnea.
- **Cardiovascular:** dizziness, weakness, syncope, chest pain, palpitations
- **Gastrointestinal:** dysphagia, nausea, vomiting, diarrhea, bloating, cramps
- **Neurologic:** headache, dizziness, blurred vision, and seizure
- **Miscellaneous:** metallic taste, feeling of impending doom

SIGNS:

- **Respiratory:** Angioedema, laryngeal edema, loss of voice, dysphonia, wheeze
- **Cardiovascular:** Tachycardia, hypotension, shock
- **Cognitive:** Depressed conscious level
- **Cutaneous:** Urticaria, pruritis, erythema, edema
- **Gastrointestinal:** Vomiting, diarrhea, abdominal distension

MANAGEMENT:

- Secure circulation, airway and breathing.
- Oxygen as needed.
- Cardiac monitoring in case of severe reactions.
- Intravenous fluid boluses
- Remove the source of antigen if possible
- Administer **1:1000 epinephrine**(0.5 – 1 mg) intramuscularly in anterolateral thigh.
- Inhaled beta-2 adrenergic agonists like salbutamol if epinephrine fails.
- Give H1- and H2-receptor blocker drugs to block histamine-mediated complications.
- **H1-blockers:** DIPHENHYDRAMINE 25 mg PO q6h, HYDROXYZINE 25 mg PO q8h, FEXOFENADINE 180 mg/day, LORATIDINE 10 mg/day, CETIRIZINE 10 mg/day
- **H2-blockers:** RANITIDINE 150 mg PO q12h or 50 mg IM/IV q6-8h, CIMETIDINE 300 mg PO QID
- Corticosteroids to prevent late-phase reaction.
- Long term prophylaxis to prevent recurrences with antihistamines and steroids (PREDNISONE 1 mg/kg/day in divided doses).

9.3. URTICARIA AND ANGIOEDEMA

Urticaria aka hives or nettle-rash

"Raised, well-circumscribed pruritic areas of erythema and edema involving dermis and epidermis are referred to as urticaria."
"Angioedema is swelling of dermis, subcutaneous or submucosal tissues due to vascular leakage."

QUICK FACTS: URTICARIA AND ANGIOEDEMA	
Pathology:	**Exposure to precipitants → degranulation of mast cells → histamine and other mediators cause leaky and sub-dermal capillaries**
Presentation:	**Urticarial: erythematous wheals with central blanching, itching, dermographism** **Angioedema: swelling of lips and other body parts**
Diagnosis:	**Clinical diagnosis** **Rule out hypothyroidism, autoimmune diseases, vasculitis, hereditary angioedema**
Treatment:	**Acute: H1 and H2 anti-histamines → tranexamic acid, epinephrine for systemic symptoms, steroids if unresponsive** **Chronic: as above, immunosuppressants for urticarial vasculitis** **Hereditary angioedema: C1 esterase inhibitor concentrate, FFP or tranexamic acid** **Kallikrein inhibitors, bradykinin 2 receptor antagonists**

- Both conditions may occur together or separately.
- Urticaria may be acute (<6 weeks) or chronic (>6 weeks).
- Conventional urticaria usually lasts <48 hours while vasculitic urticaria lasts >72 hours.

Table 9.2: FEATURES SUGGESTING VASCULITIC URTICARIA
Pain lesions
Duration of lesions >24 hours
Are associated with bruising or develop bruise on resolution
Residual hyperpigmentation

PRECIPITANTS:

- Precipitants for physical urticaria include stress or heat (cholinergic urticaria), cold (cold urticaria), deep pressure (delayed pressure urticarial), exercise, sunlight (solar urticaria), water (aquagenic urticaria), emotional stress, medications, iv radio-contrasts, certain foods, perfumes, hair dyes, detergents, dust, dander, nickel, rubber, latex.
- Other causes include allergies (to drugs, foods), infections, insects, transfusion reactions, malignancy, mastocytosis or idiopathic.

PATHOPHYSIOLOGY:

- Exposure to precipitant → degranulation of mast cells → release of histamine and other mediators → leaky derma and sub-dermal capillaries → swelling.
- In hereditary angioedema and ACE inhibitor-induced angioedema main chemical mediator is bradykinin.

SYMPTOMS AND SIGNS:

Urticaria:

- Raised discrete erythematous areas (wheals) with central blanching. There is associated itching and swelling.
- Dermographism (lesions appear on scratching)
- Urticarial lesions spare palms and soles.

Angioedema:

- Swelling of lips, eyes, tongue, hands, feet, face and scrotum (erythema may or may not be present).
- May involve respiratory, gastrointestinal and urogenital mucosa.
- Stridor or dysphonia due to laryngeal edema

- Abdominal pain and in severe cases signs of bowel obstruction.
- Urticaria may or may not be present. Systemic anaphylaxis sometimes follows severe angioedema.

INVESTIGATIONS:

- Evaluate chronic urticarial by doing CBC, ESR, TSH and ANA.
- Punch biopsy if needed to exclude vasculitis.
- Skin testing for antigens
- Prevocational challenge tests
- Complement levels
- For angioedema without urticaria (specially recurrent episodes) send C4, C1 esterase inhibitor and C1q levels. C4 can be used to screen for hereditary angioedema.

TREATMENT:

- Acute urticaria:
    - Give a non-sedating second-generation H1 anti-histamine. If symptoms are not controlled then increase dose or add a first-generation H1 anti-histamine. H2 anti-histamines have a synergistic effect if added.
    - Consider tranexamic acid in anti-histamine resistant angioedema.
    - If angioedema or systemic symptoms, give EPINEPHRINE 0.3 mg (1:1000) IM STAT. Epinephrine can be repeated every 10 – 15 minutes if necessary. Patients may need intubation or tracheostomy.
    - In case of bronchospasm nebulize with SALBUTAMOL 5 mg neb STAT.
    - Administer iv fluids especially if hypotensive.
    - Consider short term steroids in severe cases especially those non-responsive to epinephrine.
- Chronic urticaria:
    - Give non-sedating H1 anti-histamines. If symptoms are not controlled then increase dose or add a first-generation H1 anti-histamine. H2 anti-histamines have a synergistic effect if added.
    - Consider tranexamic acid in anti-histamine resistant angioedema.
    - Steroids should be used for short period in those who are non-responsive. If long-term steroids are required then start cyclosporine.
- For urticarial vasculitis use METHOTREXATE, COLCHICINE, DAPSONE, INDOMETHACIN OR HYDROXYCHLOROQUINE.
- For patients with a known history of hereditary angioedema, C1 esterase inhibitor concentrate should be given. Other options include FFPs or tranexamic acid.
- If patient is taking ACE inhibitors/ ARBs (ACEI/ ARB induced angioedema), stop these and avoid in future.
- C1 inhibitor, FFPs, ecallantide, icatibant and androgens (danazol, oxandrolone) have been used for prophylaxis.
- Medicines:
    - First-generation H1 anti-histamines (sedating):
        - CHLORPHENIRAMINE 24 mg PO OD
        - DIPHENHYDRAMINE 25 – 50 mg PO QID
        - HYDROXYZINE 40 – 200 mg PO daily
        - CYPROHEPTADINE 8 – 32 mg PO daily
    - Second-generation H1 anti-histamines (non-sedating):
        - CETIRIZINE 5 – 10 mg PO daily
        - LEVOCETIRIZINE 5 mg PO daily
        - LORATADINE 10 mg PO OD
        - DESLORATADINE 5 mg PO OD
        - FEXOFENADINE 180 mg PO OD
    - H2 anti-histamines
        - CIMETIDINE 400 mg PO twice daily or 400 – 800 at night
        - FAMOTIDINE 20 mg PO twice daily or 20 – 40 mg at night
        - RANITIDINE 150 mg PO twice daily or 300 mg at night
        - NIZATIDINE 150 mg PO twice daily or 300 mg at night

- Leukotriene receptor antagonists:
  - MONTELUKAST 10 mg PO OD
  - ZAFIRLUKAST 20 mg BID
- Other treatment options for urticaria include:
  - DOXEPIN (TCA with combined H1 and H2 anti-histamine action) 25 – 50 mg at bed-time or 10 – 25 mg 3 – 4 times daily.
  - OMALIZUMAB
  - Glucocorticoids e.g. PREDNISONE 40 – 60 mg daily for 5 days
  - C1 esterase inhibitors
  - Ecallantide (kallikrein inhibitor)
  - Icatibant (bradykinin 2 receptor antagonist)

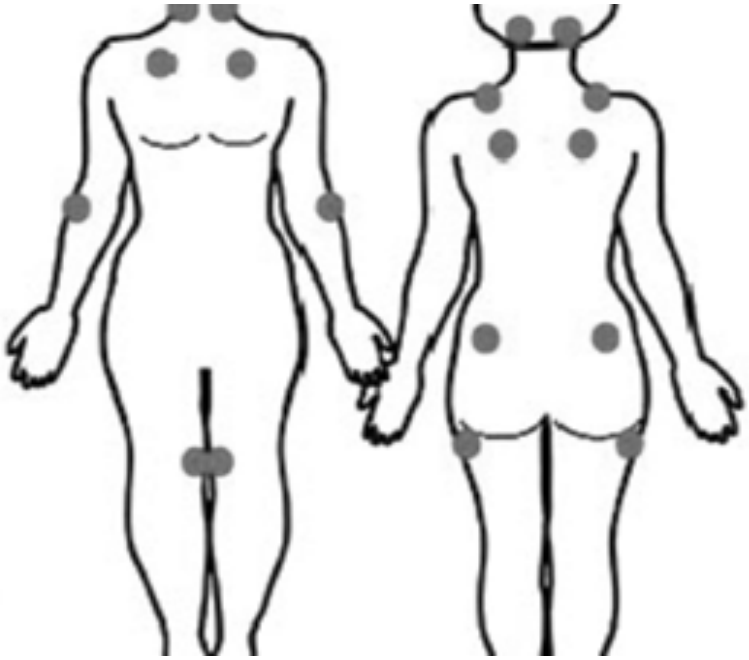
⇨ ***Angioedema without urticaria usually suggests ACEI/ ARB induced angioedema, hereditary angioedema (hereditary C1 INH deficiency) or acquired C1 INH deficiency.***

⇨ ***Angioedema with urticaria usually includes allergies to foods, mediations, infections, etc.***

9.4. FIBROMYALGIA

"It is a syndrome of chronic widespread pain and tenderness accompanied by fatigue, sleep and mood disturbances."

QUICK FACTS: FIBROMYALGIA	
Pathology:	**Increased central sensitivity to pain**
Presentation:	**Chronic aches and stiffness, fatigue, disturbed sleep, tender trigger points Associated IBS, migraine, TMJ disorder, painful bladder syndrome, reduced delta sleep**
Diagnosis:	**Diagnosis of exclusion**
Treatment:	**Patient education, psychologic/ behavior therapy Opioid analgesics, anti-anxiety agents, skeletal muscle relaxants, anti-depressants, anti-convulsants**



EPIDEMIOLOGY:

- Females > Males
- Young or middle-age

RISK FACTORS:

- Hypothyroidism, rheumatoid arthritis, sleep apnea in males

PATHOGENESIS:

- Increased central sensitivity to pain (abnormal pain processing)

PRESENTATION:

- Symptoms: Chronic aches and stiffness of whole body particularly around neck, shoulders, back and hips, fatigue, disturbed sleep, mood disturbances, cognitive difficulties
- Signs:
    - Trigger points of pain produced by palpation e.g. trapezius, medial fat pad of knee, lateral epicondyle of elbow
- Associations: irritable bowel syndrome, migraine and other headaches, temporo-mandibular joint disorders, painful bladder syndrome, reduced delta sleep, tension headache

INVESTIGATIONS:

- It is a diagnosis of exclusion.
- Rule out hypothyroidism, iron deficiency anemia, hypomagnesemia, vitamin D deficiency, hemochromatosis, rheumatoid arthritis, SLE, polymyalgia rheumatica, other autoimmune diseases.
- Anti-polymer antibody assay: positive in half of patients.
- Fibromyalgia Intensity Score (FIS) calculated at 18 tender-points varying from 0 – 10. The score can also be used for monitoring. See diagram
    - 18 standard tender points of fibromyalgia: both right and left sides of occiput at nuchal ridge, trapezius, supraspinatus, gluteal, low cervical, second rib, lateral epicondyle, greater trochanter and medial knee
    - Control sites: forehead, distal middle third of right forearm and nail of left thumb

Table 9.3: AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) MODIFIED DIAGNOSTIC CRITERIA FOR FIBROMYALGIA 2010

(Presence of all three of following criteria is needed for diagnosis)

1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3 – 6 and SS scale score ≥9.
2. Similar symptoms have been present for at least 3 months.
3. Absence of any other diagnosis to explain the symptoms.

WPI: (0 – 9)

One point is assigned for each area i.e. left shoulder girdle, right shoulder girdle, left upper arm, right upper arm, left lower arm, right lower arm, left hip, right hip, left upper leg, right upper leg, left lower leg, right lower leg, left jaw, right jaw, chest, abdomen, upper back, lower back, neck

SS Scale score: (0 – 12)

1. Fatigue → 0 = no problem 1 = slight or mild problems 2 = moderate problems 3 = severe problems
2. Waking unrefreshed → 0 = no problem 1 = slight or mild problems 2 = moderate problems 3 = severe problems
3. Cognitive symptoms → 0 = no problem 1 = slight or mild problems 2 = moderate problems 3 = severe problems
4. Severity of somatic symptoms (muscle pain, irritable bowel syndrome, fatigue/ tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/ change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms) → 0 = no symptoms, 1 = few symptoms, 2 = moderate number of symptoms 3 = great deal of symptoms

Table 9.4: AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) MODIFIED DIAGNOSTIC CRITERIA FOR FIBROMYALGIA 2016 REVISION

(Presence of all of following criteria is needed for diagnosis)

1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3 – 6 and SS scale score ≥9.
2. Similar symptoms have been present for at least 3 months.
3. Generalized pain, defined as pain in at least 4 of 5 regions.
4. Diagnosis is valid irrespective of other diagnoses.

MANAGEMENT:

- Patient education

- Well-balanced diet
- Management of stress
- Regular aerobic exercises
- Sleep therapy
- Psychologic/ behavioral therapy
- Medications:
    - Analgesics e.g. TRAMADOL
    - Anti-anxiety agents e.g. ALPRAZOLAM, CLONAZEPAM, ZOLPIDEM, ZALEPLON, TRAZODONE, BUSPIRONE
    - Skeletal muscle relaxants e.g. CYCLOBENZAPRINE
    - Antidepressants e.g. AMITRIPTYLINE 10 mg PO at night and increased to 50 mg as needed, DULOXETINE
    - Anticonvulsants e.g. PREGABALIN, GABAPENTIN
    - Other agents e.g. vitamins, minerals,

9.5. OSTEOARTHRITIS

Degenerative joint disease

"It is a degenerative disorder of joint cartilages with peri-articular bone hypertrophy and minimal inflammation and no systemic involvement."

QUICK FACTS: OSTEOARTHRITIS	
Pathology:	**Degeneration on joint cartilage → peri-articular bone hypertrophy**
Presentation:	**Joint stiffness, joint pain, bony deformities, limitation of movements Crepitus, Heberden and Bouchard nodes, flexion contracture of knee**
Diagnosis:	**Clinical diagnosis supported by radiography**
Treatment:	**Analgesics, intra-articular steroids, intra-articular sodium hyaluronate Joint replacement surgery**

RISK FACTORS:

- Advanced age; female gender; obesity; participation in contact sports; overuse of a joint; rheumatoid arthritis; metabolic diseases (hyperparathyroidism, hemochromatosis); neurologic diseases (e.g. syringomyelia, diabetes).

PRESENTATION:

- Symptoms:Joint stiffness (usually transient); joint pain (worse on movement or weight bearing and relieved by rest); deformities; limitation of movement; no systemic signs.
- Signs:Pain in joint without signs of inflammation; crepitus on passive movement; decreased range of motion of joint; bony deformities; Heberden nodes (bonny enlargement of DIP) and Bouchard nodes (bony enlargement of PIP); flexion contracture or varus deformity of knee.

RADIOLOGIC FINDINGS:

- Narrow joint space; presence of osteophytes; lipping of marginal bone; increased density of subchondral bone; bony cysts; no ankylosis.

TREATMENT:

- Weight loss
- Moderate physical activity
- Hydrotherapy
- Analgesices like ACETAMINOPHEN
- NSAIDs topical or oral (preferably topical e.g. DICLOFENAC 1% gel 4 g QID).
- Chronic oral NSAIDs should be avoided because of their long-term side-effects like peptic ulcer disease, osteoporosis and renal failure.
- CAPSAICIN 0.025 – 0.075% cream topically TDS to QID.
- TRIAMCINOLONE 20 – 40 mg intra-articularly can be used up to 4 times a year for knee osteoarthritis with effusion.
- SODIUM HYALURONATE intra-articular injection in some.

- CHONDROITIN SULFATE and/or GLUCOSAMINE are not effective.
- Total hip or knee replacement can be done for severe unresponsive disease.

⇨ ***Osteoarthritis is the most common joint disease.***

9.6. METABOLIC AND ENDOCRINE DISEASES ASSOCIATED WITH RHEUMATIC DISEASES

9.6.1. GOUT AND GOUTY ARTHRITIS

"Gout is a recurrent inflammatory arthritis caused by crystallization of monosodium urate crystals in joints which ultimately leads to deforming arthritis and is usually associated with hyperuricemia."

QUICK FACTS: GOUT AND GOUTY ARTHRITIS	
Pathology:	**Monosodium urate crystal deposition in joints → inflammatory arthritis**
Presentation:	**Asymptomatic hyper-uricemia** **Acute gouty arthritis: acute inflammatory arthritis** **Chronic gouty arthritis: chronic arthritis with deposition of tophi** **Uric acid stones** **Urate nephropathy: interstitial deposition of urate**
Diagnosis:	**Serial serum uric acid; Joint fluid aspiration and polarized light microscopy** **Radiographs**
Treatment:	**Acute gouty arthritis: NSAIDs, colchicine, steroids** **Chronic gouty arthritis: uricosuric drugs, xanthine oxidase inhibitors, uricase**

Table 9.5: CAUSES OF HYPERURICEMIA

PRIMARY HYPERURICEMIA	Over-production	Idiopathic Lesch-Nyhan syndrome (HGPRT deficiency) Glycogen storage disease
	Under-excretion	Idiopathic
SECONDARY HYPERURICEMIA	Over-production	Myeloproliferative disorders Lymphoproliferative disorders Disseminated malignancies Chronic hemolytic anemia Cytotoxic drugs e.g. cyclosporine Psoriasis
	Under-excretion	Chronic kidney disease Drugs e.g. low dose aspirin, thiazides. Hyperlacticacademia (e.g. lactic acidosis, alcoholism) Hyperketoacidemia (diabetic ketoacidosis, starvation) Diabetes insipidus Bartter syndrome

PATHOPHYSIOLOGY:

Hyper-uricemia occurs because of two main reasons:

- Decreased urate excretion
- Increased urate production

Due to hyper-uricemia, urate crystals get deposited in joints. IgGs bind to urate crystals and the complex is phagocytozed by neutrophils. The neutrophils then secrete cytokines and inflammatory mediators and lead to inflammation.

⇨ ***A tophus is a nodular deposit of monosodium urate monohydrate crystals with an associated foreign body reaction. Tophi are found in cartilages, subcutaneous and peri-artcular tissues, tendon, bone, kidneys, etc.***

CLINICAL PRESENTATIONS:

- Asymptomatic hyper-uricemia:

- 95% of patients are asymptomatic and should not be treated.

- Acute gouty arthritis:
  - Sudden onset of severe pain in a joint with erythema, swelling, tenderness and warmth and ultimately desquamation of the skin. There may be intense itching of the joint. Involvement is usually mono-articular but can asymmetrically involve multiple joints.
  - Mostly first metatarsophalangeal joint (podagra) is involved. Other joints include ankles, knees, elbow, wrist, fingers, midfoot, olecranon bursa. The arthritis tends to recur with asymptomatic periods in between and ultimately evolves into chronic deforming arthritis.
- Chronic gouty arthritis:
  - Some patients may develop a chronic arthritis with deposition of tophi in different tissues.
- Uric acid stones:
  - Uric acid stones develop in 5 – 10% of patients with gouty arthritis. Urate stones are radiolucent.
- Urate nephropathy:
  - Urate crystals may deposit in renal interstitium and lead to chronic renal insufficiency. Acute reversible renal failure may occur in patients with massive urate production (e.g. tumour lysis syndrome) due to crystal deposition tubules.

INVESTIGATIONS:

- Serial serum uric acid is usually elevated (>7.4mg/dl). Single reading is unreliable.
- Neutrophilia is seen in CBC.
- Joint fluid analysis shows increased number of neutrophils as well as negatively birefringent needle-shaped urate crystals on polarized light microscopy.
- Radiographs show ***rat-bite appearance*** (punched-out erosions with over-hanging margins of cortical bone which may be seen near tophi) in late disease.

TREATMENT:

- Asymptomatic hyper-uricemia:
  - It does not need treatment.
- Acute gouty arthritis:
  - NSAIDS are the first-line drugs for acute gout. Always check for contraindications of NSAIDS. If contraindicated, use corticosteroids. Treatment should be instituted as soon as patient perceives an attack. It is continued for 2 – 3 days after the resolution of symptoms in case of NSAIDs. Corticosteroids should be tapered more slowly.
  - Urate lowering therapies should not be instituted during the acute attack because they can precipitate attack.
  - INDOMETHACIN 25 – 50 mg PO TID until attack resolves.
  - CELECOXIB 200 mg PO BID on day 1 then 100 mg PO BID until symptoms resolve (in patients with high risk of GI bleed).
  - COLCHICINE 0.6 mg every hour until symptoms subside or a maximal dose of 4 mg.
  - METHYLPREDNISOLONE 40 mg/ day IV and tapered over 7 days.
  - PREDNISONE 40 – 60 mg/ day PO and tapered over 7 days.
  - TRIAMCINOLONE 10 – 40 mg intra-articular injection can be used in case of mono-articular involvement.

⇨ ***Interleukin-1 receptor antagonists (like anakinra, canakinumab) have also been found effective in treatment of acute gout.***

- Management of chronic gout:
  - Minimize urate production and increase urate excretion to prevent acute flares and chronic tophaceous arthritis. Keep uric acid levels <6 mg/dl.
  - Weight loss
  - Avoid alcohol
  - Dietary modifications: avoid high-purine foods like red-meat, meat extracts, sea-foods, beans, peas, lentils, spinach, cauliflowers, mushrooms; increase dairy foods; drink plenty of water.
  - Avoid medications which promote hyperuricemia: avoid thiazides, loop diuretics, low-dose aspirin and niacin.

- COLCHICINE 0.6 mg PO OD –BID can be used to suppress future attacks. Dose is reduced in renal failure.
- Serum uric acid levels can be suppressed by using: uricosuric drugs, xanthine oxidase inhibitors or uricase. Do not treat asymptomatic hyperuricemia with infrequent attacks.
- Uricosuric drugs include probenecid, sulfinpyrazone and high dose aspirin (>3 g/day). If given along with colchicine they may lessen the frequency of occurrences.
- Xanthine oxidase inhibitors include allopurinol and febuxostat. These may precipitate an acute attack of gout, therefore low dose colchicine is administered concomitantly.
- Uricase is an enzyme which convert uric acid into a readily soluble allantoin. A recombinant uricase Pegloticase can be administered intravenously to patients with refractory chronic tophaceous gout. It can cause a severe anaphylactic reaction.
- PROBENECID 0.5 g PO daily
- SULFINPYRAZONE 100 mg PO daily (starting dose). May increase up to 800 mg/day in divided doses.
- ALLOPURINOL 100 mg PO daily (maximum dose 800 mg/ day). Adjust in renal failure.
- FEBUXOSTAT 40 mg PO daily up to maximum 120 mg/ day.
- PEGLOTICASE 8 mg intravenously every 2 weeks.

Table 9.6: ALGORITHM FOR MANAGEMENT OF CHRONIC GOUT			
Order a 24-hour urine uric acid	<800 mg/ day (under-secretion)	Renal function preserved	Administer uricosuric drugs
		Renal function compromised ()	Administer xanthine oxidase inhibitors
	>800 mg/day (over-production)		Administer xanthine oxidase inhibitor

Table 9.7: COMMON SIDE-EFFECTS OF ANTI-GOUT MEDICINES				
COLCHICINE	**PROBENECID**	**SULFINPYRAZONE**	**ALLOPURINOL**	**FEBUXOSTAT**
Nausea Vomiting Diarrhea Fatigue Renal failure Peripheral neuropathy Azoospermia	Headache Nausea Vomiting Uric acid stones Bone marrow suppression	Nausea Heartburn Tinnitus Bone marrow suppression	Rash Nausea Renal failure Steven-Johnson syndrome	Arthralgia Liver injury Nausea Rash

Table 9.8: CRYSTAL INDUCED ARTHRITIS AND ARTHROPATHIES	
NAME OF CRYSTAL	**CRYSTAL-INDUCED ARTHROPATHY**
Monosodium urate (MSU)	Gout
Calcium pyrophosphate dihydrate (CPPD)	Pseudogout/ chondrocalcinosis
Calcium hydroxyapatite	Calcific periarthritis/ tendinitis
Calcium oxalate aluminium phosphate	Arthritis in dialysis patients

9.6.2. CHONDROCALCINOSIS/ PSEUDOGOUT

"It is an inflammatory/ degenerative joint disease caused by deposition of calcium pyrophosphate dihydrate crystals in joints."

QUICK FACTS: CHONDROCALCINOSIS	
Pathology:	**Calcium pyrophosphate dehydrate crystal deposition in joints**
Presentation:	**Asymptomatic, pseudo-gout, degenerative arthropathy resembling osteoarthritis, pseudo-rheumatoid arthritis**
Diagnosis:	**Synovial fluid analysis, radiographs**
Treatment:	**NSAIDs, colchicine, intra-articular triamcinolone**

- It is mostly seen in elderly patients.

PRESENTATIONS:

1. Asymptomatic: incidental finding on radiographs.

2. Pseudo-gout: it is an acute inflammatory arthritis. It usually involves multiple joints. Most commonly knees are involved.
3. Degenerative arthropathy resembling osteoarthritis. It commonly involves knees, wrists, MCP, hips and shoulders.
4. Pseudo-rheumatoid arthritis: chronic inflammatory polyarthritis with synovitis which resembles rheumatoid arthritis.

RISK FACTORS:

- Ageing; primary hyperparathyroidism; hemochromatosis; ochronosis; diabetes mellitus; hypothyroidism; Wilson's disease; chronic gout; hereditary factors.

INVESTIGATIONS:

- Synovial fluid analysis: positively birefringent rhomboid crystals on polarized microscopy.
- Radiographs: chondrocalcinosis, asymmetric joint narrowing, osteophytes, cysts.

TREATMENT:

- NSAIDs
- Colchicine prevents recurrent attacks.
- Aspiration of joint fluid and intra-articular triamcinolone in severe cases.

9.6.3. CALCIFIC PERIARTHRITIS/ TENDINITIS

"It is an inflammatory disease caused by calcium hydroxyapatite crystals deposition in peri-articular tissues and tendons."

PRESENTATION:

- Joint pains, frozen shoulder

INVESTIGATIONS:

- X-raysshow calcific deposits

MANAGEMENT:

- NSAIDs, local steroids injections for acute arthritis, extra-corporeal shock-wave therapy, surgical removal

9.6.4. ENDOCRINE DISEASES ASSOCIATED WITH RHEUMATISM

These include:

- Diabetes mellitus
- Acromegaly
- Hyperparathyroidism
- Thyroid diseases

9.7. SEPTIC ARTHRITIS

"It is an acute infectious arthritis caused by direct invasion of joint space by micro-organisms."

QUICK FACTS: SEPTIC ARTHRITIS	
Pathology:	**Acute infection and direct invasion of joint space**
Presentation:	**Gonococcal: fever, joint pain, skin lesions, septic bursitis** **Non-gonococcal: inflamed joints, erythema, fever**
Diagnosis:	**Synovial fluid analysis and culture, blood culture** **Imaging**
Treatment:	**Antibiotics: penicillin + gentamicin, 2nd or 3rd generation cephalosporins** **Add azithromycin or doxycycline for chlamydia** **Add rifampicin or long-term fluoroquinolones for prosthetic joints** **Needle aspiration, arthroscopic drainage**

COMPARE:

- Reactive arthritis which is a sterile inflammatory reaction caused by extra-articular infection and is associated with HLA-B27.

TYPES:

- Gonococcal arthritis
- Non-gonococcal arthritis
    - Suppurative
        - Neisseria gonorrhea
        - Staphylococcus aureus
        - Streptoccus species e.g. S. viridans, S. pneumonia, group B streptococci
        - Pseudomonas
        - Serratia
        - Aeromonas
        - Polymicrobial infections
    - Non-suppurative
        - Borrelia burgdorferi (Lyme disease)
        - Mycobacteria
        - HIV, lymphocytic choriomeningitis virus, hepatitis A, B and C viruses, parvovirus B19, rubella virus
        - Fungi e.g. Histoplasma, Sporothrix, Coccidioides

PATHOGENESIS:

Infection is acquired by:

- Direct inoculation (e.g. injection, trauma)
- Contiguous spread from infection of surrounding structures
- Hematogenous spread

PRESENTATION:

- Gonococcal (dermatitis-arthritis syndrome):
    - Fever
    - Joint pains (usually multiple; usually hand joints although knee, wrist, ankle and elbow are commonly affected)
    - Skin lesions (papules, pustules, pustules, ulcerations)
    - Septic bursitis (commonly olecranon or pre-patellar bursitis)
- Non-gonococcal: inflamed joints (usually single mostly knees, others include hip, shoulder and ankle), erythema, swelling, fever (usually low-grade), chills, decreased range of motion

INVESTIGATIONS:

- Synovial fluid analysis:
    - Usually WBCs >50,000/µL
    - >75% neutrophils
    - Negative for crystals
- Synovial fluid and tissue cultures
- Blood cultures
- Workup for causative organisms e.g. PCR
- CRP and ESR: raised
- Imaging: peri-articular soft tissue swelling, peri-articular osteoporosis, osteomyelitis

MANAGEMENT:

- Antibiotics: usually PENICILLIN (e.g. OXACILLIN) + GENTAMICIN or 2nd or 3rd generation CEPHALOSPORINS (CEFIXIME, CEFTRIAXONE) then adjusted according to cultures. Antibiotics are usually given intravenously for 3 – 4 weeks except gonococcal infection in which treatment is given for 2 weeks and may be switched to oral. VANCOMYCIN or LINEZOLID can be added for MRSA.
    - Gonococcal infections:

        - For concomitant chlamydia infection add AZITHRMOYCIN 2 g single dose or DOXYCYCLINE twice weekly for 7 days
    - Native joint infections:
        - usually 2 weeks IV antibiotics
        - 4 weeks in case of Staphylococci
    - Prosthetic joint infections:
        - Add RIFAMPIN
        - Consider long-term fluoroquinolones
- Pain-relief
- Joint mobilization after 5 days of therapy if there is response
- Physiotherapy
- Needle aspiration (for significant fluid)
- Arthroscopic or surgical drainage

⇨ ***Most common cause of septic arthritis in adults and children (>2 years of age) is Staphylococcus aureus.***

⇨ ***Most common cause of septic arthritis in sexually active young adults is gonococcal arthritis.***

⇨ ***Most common cause of early prosthetic joint infections is Staphyloccus aureus and most common cause of late prosthetic joint infections are coagulase negative staphylococci.***

9.8. SYSTEMIC CONNECTIVE TISSUE DISORDERS

9.8.1. RHEUMATOID ARTHRITIS (RA)

"It is a chronic symmetric inflammatory synovitis and arthritis."

QUICK FACTS: RHEUMATOID ARTHRITIS	
Pathology:	**Unknown trigger → autoimmune reaction → synovitis amd arthritis → pannus formation → cartilage and bone destruction → deformities**
Presentation:	**Low-grade fever, arthralgias, malaise, weakness, weight loss** **Symmetric polyarthritis leading to deformities** **Cutaneous features, pleuritis, pleural effusion, pulmonary fibrosis, rheumatoid nodules, pericarditis, pericardial effusion, valvular incompetency, scleritis, scleromalacia, neuropathies, normocytic anemia, Felty's syndrome**
Diagnosis:	**RA factor, anti-CCP, anti-SA, anti-MCV, ANA, X-rays**
Treatment:	**NSAIDs → steroids → DMARDs** **TNF inhibitors, Surgical treatment**

EPIDEMIOLOGY:

- Age: any age (usually 40 – 50 years for females and 60 – 80 years for males)
- Gender: Male:Female ratio = 1:3
- Genetics: HLA DR4

PATHOPHYSIOLOGY:

- External trigger (? Infection) → autoimmune reaction (both cell-mediated and antibody-mediated) → synovitis and arthritis with cytokine secretion → pannus formation → cartilage destruction and bone erosion eventually destroys joints leading to deformities

POOR PROGNOSTIC FACTORS:

- Increased disease activity scores, presence of erosions, smoking, delayed diagnosis or treatment, genetic predisposition (e.g. HLA DR4), MRI bone edema, high titers of RF or anti-CCP, insidious onset, female gender, extra-articular features

PRESENTATION:

- Onset is usually insidious.
- General features: low-grade fever, malaise, arthralgias, weakness, weight loss
- Joint involvement:
    - Persistent symmetric polyarthritis

    - Preferably involves small joints of hands and feet (sparing DIP), wrists, elbows, shoulders, ankle, knees, hips, atlantoaxial joint and temporomandibular joint. Axial joints (except atlantoaxial joint) and DIP joints are spared.
    - Joints are red, swollen, warm, painful, with limited range of movement.
    - Typically there is morning stiffness which lasts more than half an hour. Stiffness improves with movement and returns upon rest.
    - Progressive joint destruction leads to deformities.
    - Characteristic deformities include:
        - Fingers: swan-neck deformity, button-hole deformity (boutonniere deformity), mallet finger, ulnar deviation at MCP joints
        - Thumbs: hitch-hiker thumb deformity (Z-deformity)
        - Toes: claw-toe deformity
        - Wrist: radial deviation at wrist
    - Flexor tenosynovitis occurs
    - Atlanto-axial subluxation may lead to cervical cord compression.
- Extra-articular involvement:
    - Cutaneous features: thin atrophic skin, easy bruising, subcutaneous rheumatoid nodules (occur on elbows, sacrum, scalp in 30 40% patients), palmar erythema, vasculitis/ ulcerations involving fingers and nail-folds
    - Pulmonary features: pleuritis (most common pulmonary feature), pleural effusions (See 5.4.1.), lower lobe predominant pulmonary fibrosis (interstitial lung disease), pulmonary rheumatoid nodules
    - Cardiac features: pericarditis (most common cardiac feature), pericardial effusion, conduction abnormalities (due to rheumatoid nodules), valvular incompetence (mostly mitral regurgitation)
    - Ocular features: scleritis, scleromalacia, dry eyes and associated Sjogren syndrome
    - Nervous features: mononeuritis multiplex, nerve entrapment (mostly carpal tunnel syndrome)
    - Hematologic features: normocytic normochromic anemia (most common hematological feature), thrombocytosis, Felty's syndrome (triad of rheumatoid arthritis, neutropenia, splenomegaly which ,may also include leucopenia, thrombocytopenia and lymphadenopathy)
    - Vasculitic features: microvascular vasculitis (mesenteric vasculitis, PAN, etc)
    - Renal features: membranous nephropathy, secondary amyloidosis
- Complications:
    - Cervical spine instability → myelopathy
    - Frequent infections
    - Amyloidosis
    - Increased risk of lymphoma
- Associations: Sjogren's syndrome, pneumoconiosis, overlap syndromes, osteoporosis, hypoandrogenism

INVESTIGATIONS:

- CBC: normocytic anemia, thrombocytosis
- ESR, CRP: raised
- RA factor (IgM or IgA antibody against fixed portion of IgG): 50 – 80% sensitive, 85 – 90% specific. It is present in 100% of patients with extra-articular features.
- Antibody to cyclic citrullinated peptide (Anti-CCP): 41% sensitive, 98% specific
- Other antibodies:
    - ANA (20%)
    - Antibodies against citrullinated vimentin (anti-SA)
    - Antibodies against mutated citrullinated vimentin (anti-MCV)
- Radiographs: juxta-articular osteoporosis, narrowing of joint space, bony erosions
- Synovial fluid analysis: inflammatory nature (usual white cell count is 5000 – 50,000 WBCs/μL mostly neutrophils)
- Joint imaging:

- X-ray findings are mostly seen in wrists, hands and feet. These include periarticular osteopenia, soft tissue swelling, symmetric joint space loss, subchondral erosions.
- MRI more sensitive
- Ultrasound for erosions

MANAGEMENT:

Goals of treatment:

- Prevent joint deformity
- Achieve clinical remission
- Medications:
  - NSAIDs: provide symptomatic relief of joint pain.
    - Traditional NSAIDs: indomethacin, ibuprofen, diclofenac
    - COX-2 inhibitors: CELECOXIB
  - Steroids: low-dose steroids (e.g. PREDNISONE 5 – 10 mg) are used to decrease disease activity while DMARDs are taking effect.
  - Disease modifying anti-rheumatic drugs (DMARDS):
    - Early DMARD is necessary to prevent joint deformities.
    - DMARDs are usually used in combination e.g. METHOTREXATE + TNF inhibitors
    - Synthetic DMARDs:
      - METHOTREXATE 7.5 – 15 mg once weekly
      - SULFASALAZINE 0.5 g twice daily (up to 3 g/ day)
      - LEFLUNOMIDE 20 mg once daily
      - HYDROXYCHLOROQUINE 200 – 400 mg/ day
      - Others: MINOCYCLINE, AZATHIOPRINE, CYCLOSPORINE, gold salts, D-PENICILLAMINE
    - Biologic DMARDs:
      - Tumor necrosis factor/ TNF inhibitors include ETANERCEPT, INFLIXIMAB, ADALIMUMAB, GOLIMUMAB, CERTOLIZUMAB.
      - Others: ABATACEPT, RITUXIMAB, TOCILIZUMAB, ANAKINRA, SARLILUMAB
- Surgical treatment includes synovectomy
- Other therapies: orthotics, splints, exercise

Disease approach:

- Low disease activity without poor prognostic factors:
  - DMARD monotherapy
  - If disease activity still moderate-high then add second DMARD
  - If disease activity still moderate-high then add anti-TNF agents
- Low disease activity with poor prognostic factors or moderate-high disease:
  - DMARD monotherapy or combination
  - If disease activity still moderate-high then add or switch to another DMARD or anti-TNF agent or abatacept/rituximab

Table 9.9: 2010 AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS

		Points
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 (≤3 times ULN)	2
	High-positive RF or high-positive anti-CCP (≤3 times ULN)	3
Acute-phase reactants	Normal CRP ad normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1
Total score ≥6 = Definite rheumatoid arthritis		

⇨ ***Rheumatoid arthritis is the most common form of chronic inflammatory arthritis.***

⇨ ***Most specific investigation for diagnosis of rheumatoid arthritis is anti-CCP.***

⇨ ***Most common cause of death in RA is cardiovascular disease.***

Table 9.10: 2016 AMERICAN COLLEGE OF RHEUMATOLOGY DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS	
	POINTS
Joint pain with morning stiffness ≥1 hour	1
Hand (wrist, MCP, PCP) synovitis	2
Synovitis of ≥2 joints	1
Symmetric synovitis	1
Duration of ≥6 weeks for synovitis	2
Old female	1
Positive history of RA in first-degree family	1
Positive history of smoking	1
RF/ Anti-CCP positivity: • Positive RF or anti-CCP • Positive RF and anti-CCP • High titer RF and/or anti-CCP	 1 2 2
HLA-DR4 positivity	1
Involved joint imaging: • Juxta-articular osteoporosis • Erosion in x-ray or MRI	 1 2

Table 9.11: ASSESSMENT OF DISEASE SEVERITY
Disease Activity Score 28 or DAS28 score (a simplified DAS score which utilizes only 28 joints) Number of swollen joints Number of tender joints CRP or ESR Global assessment of health **Interpretation:** Total score is calculate by using DAS28 formula ≥5.1 very active disease 3.3 – 5.1 moderately active disease ≤3.2 low disease activity <2.6 remission
Disease Activity Score or DAS score (utilizes 40 joints) Ritchie Articular Index ESR General health assessment on visual analog scale **Interpretation:** Total score is calculate by using DAS formula ≤2.4 Low disease activity 2.5 – 3.7 Moderate disease activity >3.7 High disease activity
Simplified Disease Activity Index or SDAI (utilizes 28 joints) Number of tender joints Number of swollen joints Patient's and provider's global assessment of disease activity **Interpretation:** Total score is calculate by using SDAI formula 0.0 – 3.3 = remission 3.4 – 11.0 = low activity 11.1 – 26.0 = moderate activity 26.1 – 86.0 = high activity

Table 9.12: CAUSES OF RAISED RA FACTOR	
Normal population (4% of total, 25% of elderly)	**Chronic infections:** Leprosy Syphilis Bacterial endocarditis Pulmonary tuberculosis
Connective tissue disorders: Rheumatoid arthritis Sjögren syndrome SLE Scleroderma Polyarteritis nodosa Dermatomyositis	**Others:** Autoimmune liver disease Paraproteinemias Cryoglobulinemias Transplant recipients Relatives of rheumatoid arthritis patients Transiently during acute infections

9.8.2. JUVENILE IDIOPATHIC ARTHRITIS (JIA)

Aka juvenile rheumatoid arthritis

"It is a chronic inflammatory arthritis in young children."

QUICK FACTS: JUVENILE IDIOPATHIC ARTHRITIS	
Pathology:	**Autoimmune synovitis**
Presentation:	**Young patients with arthritis, high-spiking fevers, salmon-colored evanescent rash on extremities and trunks, uveitis, MAS**
Diagnosis:	**Ferritin raised** **ANA positive**
Treatment:	**NSAIDs, steroids, MTX, leflunomide, anakinra, TNF inhibitors, IL-antagonists, IL-6 inhibitors, calcineurin inhibitors**

PATHOPHYSIOLOGY:

- Autoimmune destruction of synovial joints

TYPES:

American College of Rheumatology (ACR) classification:

- Poly-articular
- Pauci-articular
- Systemic

Table 9.13: INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY (ILAR) CLASSIFICATION	
Systemic onset JIA **Aka Childhood Still's disease**	≥1 joint involved Preceded by fever of at least 2 weeks Features for ≥3 days At least one of following: evanescent rash, generalized lymphadenopathy, hepato/splenomegaly, serositis (pericardial or pleural effusion)
Oligoarticular JIA (MOST COMMON)	1 – 4 joints involved during first 6 months
Polyarticular JIA	≥5 joints during first 6 months of disease Can be RA factor positive or negative
Psoriatic arthritis	Any of the following two: Arthritis and psoriasis Arthritis and at least 2 of the following: dactylitis, nail pitting, onycholysis, first-degree relative with psoriasis
Enthesitis-related JIA	Features of enthesitis present Features of spondyloarthritis
Undifferentiated arthritis	-

RISK FACTORS:

- Exposure to antibiotics

PRESENTATION:

- Diagnostic criteria require age <16 years and duration >6 weeks, arthritis in at least one joint and not explained by any other disease.

- Arthritis:
    - Insidious or abrupt
    - Usually for ≥6 weeks
    - Associated with morning stiffness or gelling
    - Some children may not complain of joint pain but may stop using involved joints, develop contractures or limp.
- Spiking fevers (1 – 2 times per day at about the same time of day)
- Rash
    - Lasts few hours (evanescent)
    - Develops on trunk and extremities
    - Usually non-pruritic, salmon-colored macules
- Others: anterior uveitis
- Complications: macrophage-activating syndrome

Investigations:

Diagnosis is based on clinical features. There is no specific investigation.

- CBC: anemia, leukocytosis, lymphopenia, thrombocytosis
- ESR and CRP: raised
- Complement: may be low
- Ferritin: highly raised
- ANA: high in 70% (Needs exclusion of SLE)
- RA factor
- Radiography: X-rays may show soft tissue swelling, osteopenia, narrowing of joint space, bony erosions, etc. CT and MRI are more sensitive but CT may not be done due to risks of radiation-exposure.

TREATMENT:

- Systemic disease with active systemic features: ANAKINRA + systemic steroids
- Systemic disease with no active systemic features:
    - ≤4 joints involved: NSAIDs or intra-articular steroids
    - >4 joints involved:
        - First-line: METHOTREXATE, LEFLUNOMIDE
        - Second-line:
            - TNF inhibitors e.g. ABATACEPT
            - Interleukin antagonists e.g. ANAKINRA, CANAKINUMAB, RILONACEPT
            - Interleukin-6 inhibitors e.g. TOCILIZUMAB
- Systemic disease with macrophage-activating syndrome: ANAKINRA, calcineurin inhibitor or systemic steroids.

⇨ ***JIA is the most common chronic rheumatologic disease in children.***

9.8.3. ADULT STILL DISEASE

"It is a systemic form of juvenile idiopathic arthritis which occurs around 20 – 30 years of age."

QUICK FACTS: ADULT STILL DISEASE	
Pathology:	**Systemic form of JIA**
Presentation:	**High-spiking fever, sore-throat, evanescent rash, hepatosplenomegaly, lymphadenopathy, serositis, arthritis**
Diagnosis:	**Anemia, high leukocytosis, high ferritin** **Glycosylated ferritin**
Treatment:	**High dose aspirin → if refractory steroids → if still refractory TNF inhibitors, anakinra**

Table 9.14: YAGAMUCHI'S DIAGNOSTIC CRITERIA FOR ADULT-ONSET STILL'S DISEASE **Diagnosis requires five or more criteria with at least two major criteria**
Major criteria: • Fever >39 degree C, lasting ≥1 week • Arthralgia or arthritis lasting ≥2 weeks • Typical rash • Leukocytosis >10,000/µL with >80% neutrophils
Minor criteria: • Sore-throat • Recent significant lymphadenopathy • Hepatomegaly or splenomegaly • Abnormal liver function tests • Negative test for ANA and RA factor
Exclude: • Infections • Malignancies (mainly lymphoma) • Other rheumatic diseases (mainly systemic vasculitides)

CLINICAL FEATURES:

These are similar to those of systemic onset JIA i.e.

- High spiking fevers
- Sore-throat
- Evanescent rash
- Hepatosplenomegaly
- Lymphadenopathy
- Serositis
- Arthritis (occurs late and there is particularly destructive arthritis of wrists)

INVESTIGATIONS:

- Anemia
- Very high leukocytosis (up to 40,000/µL)
- Very high ferritin (usually >3000 ng/mL)
- Glycosylated ferritin (specific for the disease)

TREATMENT:

- High dose ASPIRIN PO 1 g thrice daily or other NSAIDs
- In case of no response: high-dose PREDNISONE
- In case of refractory disease: TNF inhibitors, Interleukin-1 receptor antagonist (ANAKINRA)

9.8.4. SYSTEMC LUPUS ERYTHEMATOSUS (SLE)

Aka lupus

"It is a chronic inflammatory autoimmune disorder caused by antibodies to nuclear antigens."

QUICK FACTS: SYSTEMIC LUPUS ERYTHEMATOSUS	
Pathology:	**Defective apoptosis → exposure of nuclear proteins → autoantibodies**
Presentation:	**Fever, fatigue, malaise, weight loss** **Cutaneous: butterfly rash, photosensitivity, malar rash, discoid rash, livedo reticularis** **Musculoskeletal: arthralgias, arthritis, myalgia** **Cardiac: pericarditis, myocarditis, Libman-Sacks endocarditis** **Pulmonary: pleurisy, pleural effusion, pneumonitis, pulmonary hypertension** **Hematological: cytopenias** **Renal: proteinuria, lupus nephritis** **Gastrointestinal: nausea, dyspepsia, bowel vasculitis** **CNS: seizures, headache, confusion, psychosis, neuropathies, transverse myelitis** **Associated autoimmune diseases**
Diagnosis:	**Complement levels** **ANA, anti-ds DNA, anti-Sm antibody, anti-RNP, anti-Ro, anti-La, anti-histone, anti-phospholipid**
Treatment:	**Mild: HCQ +/- NSAIDs and/or steroids → immunosuppressants if unresponsive** **Severe: Induction therapy with glucocorticoids + mycophenolate mofetil or cyclophosphamide or azathioprine → maintenance therapy with steroids + mycophenolate or azathioprine** **Supportive treatment**

PATHOGENESIS:

- Genetic predisposition (HLA DR3/2, C4 deficiency, hormone levels) or environmental triggers (UV light, microbial response, drugs) → B-cell and T-cell proliferation, high CD4:CD8 ratio, defective immune complex clearance and impaired tolerance → defective apoptosis → exposure of nuclear proteins → autoantibodies and immune complexes (type III hypersensitivity)

EPIDEMIOLOGY:

- It is 9 times more common in females.
- It is associated with sex hormones i.e. occurs in reproductive age.
- It is more common in African-American patients.

TYPES OF SLE:

- Spontaneous SLE
- Discoid lupus (skin lesions)
- Drug-induced SLE
- ANA-negative lupus

CLINICAL FEATURES:

- Constitutional features: fatigue, fever, malaise, weight loss
- Cutaneous features: butterfly rash (acute erythematous rash over cheeks and nasal bridge sparing nasolabial folds), photosensitivity, livedo reticularis, panniculitis, bullous lesions, urticarial, discoid lesions, painless oral ulcers, nasal ulcers, non-scarring alopecia, Raynaud's phenomenon, other presentations of cutaneous lupus
- Musculoskeletal features: arthralgia (usual initial feature), arthritis (rarely erosive or deforming), myalgia, avascular necrosis, Jaccoud arthropathy (chronic deforming arthritis of fingers without erosions)
- Cardiac features: pericarditis, myocarditis, Libman-Sacks endocarditis (non-infective endocarditis of mitral or tricuspid valves)

- Pulmonary features: pleurisy (most common pulmonary feature), pleural effusion (exudative with high LDH), pneumonitis, pulmonary hypertension, interstitial lung disease, pulmonary embolism, pulmonary hemorrhage, shrinking lung syndrome
- Hematological features: cytopenias e.g. leukopenia, lymphopenia, anemia, thrombocytopenia, hemolytic anemia, TTP
- Renal features: proteinuria (>0.5 g/day), glomerulonephritis (lupus nephritis), cellular casts, acute or chronic renal failure, hypertension
- Gastrointestinal features: nausea, dyspepsia, abdominal pain, bowel vasculitis, pancreatitis, bowel perforation, pseudo-obstruction
- CNS features: seizures, headache, acute confusional state, autonomic disorder, psychosis, depression, transverse myelitis, cognitive deficits, polyneuropathy, mononeuropathy, cerebrovascular disease, anxiety disorder, GBS, organic brain syndrome, aseptic meningitis
- Immunologic features: impaired immune response
- Others: conjunctivitis, fetal loss, generalized lymphadenopathy
- Associations: Sjögren's syndrome, Raynaud's, anti-phospholipid antibody syndrome

INVESTIGATIONS:

- CBC: may show cytopenias
- Creatinine and liver function tests
- For renal involvement: urine detailed report, creatinine, spot protein/spot creatinine ratio, renal ultrasound
- For joint involvement: joint effusion studies (non-inflammatory or inflammatory)
- Skin/ mucous membranes: histology, immunofluorescence
- For muscle involvement: LDH, creatine kinase
- For pulmonary involvement: chest x-ray, HRCT, PFTs, bronchoalveolar lavage
- For nervous system: EEG, MRI, CT, CSF analysis, NCV
- CRP rises with disease activity, ESR usually normal or slightly high
- Complement levels: C3 low in active disease while low C4 predisposes to SLE
- Antibodies:
    - Anti-nuclear antibodies (ANA):
        - Antibody to multiple nuclear antigens.
        - Most common antibody and best screening test.
        - Prevalence 98% but not specific.
    - Anti-double stranded DNA antibodies (Anti-ds-DNA):
        - Antibody to double-stranded DNA.
        - Prevalence 40 – 70%.
        - Their levels correlate with disease activity, nephritis and vasculitis.
    - Anti-Sm antibody:
        - Antibody to protein complexed with U1 RNA.
        - Most specific antibody.
    - Anti-ribonucleoprotein antibody (Anti-RNP):
        - High titers associated with overlap syndromes.
    - Anti-Ro (Anti-SSA) antibody
        - Associated with sicca syndrome and neonatal lupus.
    - Anti-La (Anti-SSB) antibody
        - Associated with sicca syndrome and neonatal lupus.
    - Anti-histone antibody
        - Seen in 100% of cases of drug-induced SLE.
    - Anti-phospholipid antibody
        - Antibodies to phospholipids, ß2 glycoprotein 1 cofactor and prothrombin
        - Predispose to clotting and abortions.
    - Anti-erythrocyte antibody
        - Associated with autoimmune hemolysis.
    - Anti-platelet antibody
        - Associated with thrombocytopenia.
    - Anti-neuronal antibody
        - Associated with CNS lupus.
    - Anti-ribosomal P antibody

- Associated with CNS lupus.

TREATMENT:

- The disease runs a chronic, relapsing and unpredictable course.
- Avoid triggers and flares e.g. sunlight.

Drug management:

- For no, mild and/or moderate organ manifestations:
  - First-line: HYDROXYCHLOROQUINE or CHLOROQUINE +/- NSAIDS and/or glucocorticoids
  - If no response: AZATHIOPRINE or METHOTREXATE or MYCOPHENOLATE MOFETIL
  - Adjunctive treatment: BELIMUMAB
- For severe disease or class II-IV lupus nephritis with active organ involvement:
  - Continue HYDROXYCHLOROQUINE
  - Induction therapy: glucocorticoids + MYCOPHENOLATE MOFETIL or CYCLOPHOSPHAMIDE or AZATHIOPRINE
  - Maintenance therapy: low-dose glucocorticoids + MYCOPHENOLATE MOFETIL or AZATHIOPRINE
  - For refractory cases: calcineurin inhibitors (CYCLOSPORINE A, TACROLIMUS) or RITUXIMAB
  - Immunoglobulins may be used in CNS lupus or refractory thrombocytopenia
- For pregnant patients with anti-phospholipid antibodies: PREDNISONE, ASPIRIN and anticoagulation
- For skin lesions: topical steroids or topical calcineurin inhibitors
- Adjunctive therapy: vitamin D

Monitoring:

- Evaluate disease activity
  - Clinical features
  - Standardized scores e.g. SLE Responder Index, SLEDAI, SLAM, BILAG, ECLAM scores
  - Anti-ds DNA (BEST)
- Evaluate damage e.g. SLICC/ACR damage index
- For patients receiving chloroquine or hydroxychloroquine do 6 monthly ocular examinations

DRUG-INDUCED SLE:

- It occurs equally in males and females.
- CNS and kidneys are not involved. Butterfly rash, oral ulcers and alopecia are typically not seen.
- Anti-histone antibody is present in 100%. Anti-ds DNA and Anti-Sm antibodies are absent.
- Complement levels are not low.
- Symptoms and laboratory abnormalities usually improve after stopping drug.

Table 9.15: DRUGS WHICH CAUSE SLE
Mnemonic: Listen Please Check MATT QM in SHIP

Lithium
Penicillamine
Procainamide
Chlorpromazine
Carbamazepine
Minocycline
ACE inhibitors
Tetracyclins
TNF inhibitors
Quinidine
Methyldopa
Sulfonamide
Hydralazine
Interferon alpha
Isoniazid
Phenytoin

Table 9.16: ACR REVISED DIAGNOSTIC CRITERIA FOR SLE 1992 (4 out of 11 are needed for diagnosis: sensitivity 85%, specificity 95%) ACR = American College of Rheumatology	
Mnemonic: DOPAMIN RASH	
Discoid rash	-
Oral ulcers	-
Photosensitivity	-
Arthritis	-
Malar rash	-
Immunologic abnormalities	Positive LE cell preparation OR Anti-ds DNA antibody OR Anti-Sm antibody OR False positive serology for syphilis
Neurologic disease	Seizures OR Psychosis (without any other cause)
Renal disease	Proteinuria >0.5 g/day OR Proteinuria ≥3+ on dipstick OR cellular casts
ANA	Positive ANA
Serositis	Pericarditis, Pleuritis
Hematologic disorders	Hemolytic anemia OR Leukopenia (<4000/ µl) OR Lymphopenia (<1500/ µl) OR Thrombocytopenia (<100,000/ µl)

Table 9.17: SLICC CRITERIA FOR DIAGNOSIS OF SLE 2012 (≥4 criteria are needed for diagnosis with at least one clinical and at least one laboratory criteria OR biopsy-proven lupus nephritis with positive ANA or Anti-ds DNA) SLICC = SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS	
CLINICAL CRITERIA	**IMMUNOLOGIC CRITERIA**
1. Acute cutaneous lupus (including butterfly rash) 2. Chronic cutaneous lupus 3. Oral or nasal ulcers 4. Non-scarring alopecia 5. Synovitis or tenderness of ≥2 joints with morning stiffness of ≥30 minutes 6. Serositis (pleurisy or pericardial effusion of >1 day) 7. Renal involvement (urine PCR or 24-hour urine protein >0.5 g/day) 8. Neurologic involvement 9. Hemolytic anemia 10. Leukopenia (WBC <4000/µL) or lymphopenia (<1000/ µL) 11. Thrombocytopenia (<100,000/ µL)	1. ANA 2. Anti-ds DNA 3. Anti-Sm 4. Anti-phospholipid antibodies (anticardiolipin; anti-β 2-glycoprotein I IgA, IgG or IgM; false positive VDRL) 5. Low complement (C3, C4, CH50) 6. Direct Coomb's test (in the absence of hemolytic anemia)

Table 9.18: INTERNATIONAL SOCIETY OF NEPHROLOGY AND RENAL PATHOLOGY SOCIETY'S CLASSIFICATION OF LUPUS NEPHRITIS	
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerotic lupus nephritis

⇨ ***SLE is the most common rheumatologic disorder.***

⇨ ***Most sensitive investigation for SLE is ANA.***

⇨ ***Most specific investigation for SLE is anti-ds DNA.***

⇨ ***Classic tetrad of presentation is fever, fatigue, joint pain and butterfly rash in a reproductive age group female.***

Table 9.19: CAUSES OF RAISED ANA AND ANTI DS DNA
Causes of raised ANA
Normal population (5% usually below 1:320)
Drug-induced lupus
SLE
Scleroderma
Sjögren syndrome
Mixed connective tissue disease
Polymyositis
Causes of raised anti ds DNA
SLE
Sjögren syndrome

9.8.5. ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APLAS OR APS)

"It is an autoimmune disorder characterized by hyper-coagulable state (recurrent arterial or venous thromboses) due to presence of autoantibodies."

QUICK FACTS: ANTIPHOSPHOLIPID ANTIBODY SYNDROME	
Pathology:	**Antibodies against phospholipid-binding proteins**
Presentation:	**Asymptomatic** **Thrombotic complications** **Complications in pregnancy**
Diagnosis:	**Thrombocytopenia, prolonged APTT** **Anticardiolipin antibodies, anti-beta2-glycoprotein antbodies, antiprothrombin antibodies** **Positive RPR and VDRL**
Treatment:	**Non-pregnant: life-long anticoagulation** **Pregnant: heparin + aspirin, IVIG**

PATHOPHYSIOLOGY:

Antibodies against phospholipid-binding proteins

1. Anticardiolipin antibody
2. Lupus anticoagulant
3. Antibody causing false positive VDRL

TYPES:

- Primary: occurs alone
- Secondary: occurs in association with other autoimmune disorders e.g. SLE

PRESENTATION:

- Asymptomatic
- Thromboses: DVT, PE, CVA Budd-Chiari syndrome, cerebral venous sinus thrombosis, myocardial infarction, digital infarction, etc.
- Others: altered mentation, livedo reticularis, skin ulcers, microangiopathic nephropathy, cardiac valvular dysfunction e.g. MR
- Complications in pregnancy: unexplained fetal death after first trimester, one or more premature births before 34 weeks because of preeclampsia/ eclampsia, three or more unexplained miscarriages in first trimester.
- Catastrophic APS (CAPS): rapidly progressive thromboembolic disease of three or more organs

INVESTIGATIONS:

- CBC: thrombocytopenia
- Partial thromboplastin time: prolonged
- Dilute Russell Viper venom test: prolonged coagulation which does not correct in mixing studies

- Antibody assays: anti-cardiolipin antibodies, anti-β2 glycoprotein antibodies, anti-prothrombin antibodies
- Positive rapid plasma regain (RPR) and VDRL but negative anti-treponemal assays
- Check for antibodies on two occasions at least 12 weeks apart

MANAGEMENT:

- Non-pregnant patients:
  - Lifelong anticoagulation: life-long WARFARIN (target INR 2.0 – 3.0)
  - Other options FONDAPARINUX, RIVAROXABAN
- Pregnant patients:
  - Anti-coagulation: subcutaneous HEPARIN + ASPIRIN 81 mg once daily (in case of pregnancy)
  - For preventing abortion: IVIG
  - Glucocorticoids useless
- For CAPS:
  - Anticoagulation with intravenous heparin
  - High dose corticosteroids
  - IV immunoglobulin or plasmapharesis
  - Anti-CD20 for refractory cases

9.8.6. SCLERODERMA/ SYSTEMIC SCLEROSIS

"It is a connective tissue disorder which leads to widespread fibrosis in skin and other organs."

QUICK FACTS: SCLERODERMA	
Pathology:	**Unknown trigger → cytokine production → fibroblast activation and collagen deposition → fibroproliferative vascular lesions, thickened skin**
Presentation:	**Disease can limited or diffuse** **Raynaud's phenomenon** **Cutaneous features: tightening, induration of skin, sclerodactyly** **Dysphagia, esophageal reflux, esophageal stricture** **Interstitial pulmonary fibrosis, pulmonary hypertension** **Pericardial effusion, cardiomyopathy** **Scleroderma renal crisis** **Healed pitting ulcers in fingers, telengiectasias**
Diagnosis:	**CRP, ESR: elevated** **ANA: positive** **Anti-centromere antibody (limited)** **Anti-topoisomerase I or anti-RNA polymerase I and III (diffuse)**
Treatment:	**No curative treatment** **Steroids in lung disease**

EPIDEMIOLOGY:

- Age: usually 35 – 50 years
- Gender: female: male ratio is 4:1

TYPES OF SCLERODERMA:

- Diffuse: 20%
- Limited: 80%
- CREST syndrome (a variant of limited form)
- Scleroderma without internal organ involvement: morphoea, coup de sabre

PATHOPHYSIOLOGY:

- Exposure to unknown triggers (e.g. vinyl chloride) → ? → cytokine production → activated fibroblasts → Collagenous deposition → fibro-proliferative vascular lesions, thickened skin and deposition in internal organs, altered immunity

PRESENTATION:

- Raynaud's phenomenon

    - Most common and usually initial feature
    - Vasospasm and thickening of vessel walls in digits can lead to ischemia.
    - Vasospasm can be induced by cold or stress.
    - It is relieved spontaneously or with warming of extremities.
    - There is blanching followed by cyanosis and lastly redness.
    - Severe or recurrent disease may lead to ulceration or infarction/ gangrene.
- Cutaneous features:
    - Initial swelling and puffiness following by tightening and induration of skin of face and extremities, sclerodactyly (claw-like hand), contractures, disability. There may be severe pruritis.
    - Limited form: slow involvement of extremities, face and neck sparing trunk.
    - Diffuse form: rapid and widespread involvement including trunk and proximal limbs.
- Visceral features:
    - Limited form: visceral involvement is not pronounced and is usually late in form of pulmonary hypertension, ischemic vascular disease
    - Diffuse form: involvement of GIT, lungs, heart and kidney. Pulmonary hypertension is rare.
- Gastrointestinal features: dysphagia, reflux, esophageal strictures, delayed gastric emptying, constipation/ diarrhea (bacterial overgrowth syndrome), abdominal distension, pseudo-obstruction
- Pulmonary features: interstitial fibrosis, pulmonary hypertension
- Cardiac features: pericardial effusion, cardiomyopathy, CHF, arrhythmias
- Renal features:
    - Scleroderma renal crisis: rapid development of malignant hypertension in diffuse form
- Musculoskeletal features: arthralgias, erosive arthritis, myositis
- Vascular features: healed pitting ulcers in fingers, large fingertip ulcers, telengiectasias, non-atherosclerotic MI
- Other features: peripheral edema, carpal tunnel syndrome, erectile dysfunction, dyspareunia, vaginal fibrosis, sicca syndrome
- CREST syndrome:
    - Calcinonsis
    - Raynaud's phenomenon
    - Esophageal dysmotility
    - Sclerodactyly
    - Telengiectasias (over digits and nails)

INVESTIGATIONS:

- CRP and ESR: usually elevated
- RA factor: positive in 30%
- ANA: positive in 90% (homogenous, speckled or nucleolar staining)
- Anti-centromere antibody:
    - Specific for limited form 50 – 90%
    - Positive in 10% of diffuse cases
- Anti-topoisomerase I antibody (anti-scleroderma-70 or anti Scl-70):
    - Specific for diffuse form
    - Positive in 20 – 40% of diffuse form
- Anti-RNA polymerase I and III:
    - Present in 15 – 20% of patients with diffuse disease
- CXCL4: elevation correlates with severity of pulmonary fibrosis
- Muscle enzymes: may be raised
- Radiography: calcinosis
- Nail-fold microscopy
- Barium swallow
    - Demonstrates esophageal dysmotility
- Pulmonary function tests
    - Demonstrate restrictive defect in case of fibrosis
- HRCT

MANAGEMENT:

- There is no curative treatment. Steroids are only helpful in lung disease.
- Treatment is symptomatic.
- Prognosis is poor for diffuse form and good for limited form.
- Hematopoietic stem cell transplantation.
- For musculoskeletal pain: NSAIDs, steroids, IVIGs
- For esophageal reflux: H2RBs or PPIs
- For skin disease: D-penicillamine, bovine collagen, methotrexate, mycophenolate mofetil
- For Raynaud's phenomenon:
    - Avoid triggers
    - Keep hands warm
    - Calcium channel blockers (in severe cases)
    - Prostacyclin or iloprost infusion (in severe cases)
- For pulmonary involvement: steroids, immuno-suppressants
- For renal involvement:
    - ACE inhibitors or ARBs

Table 9.20: 2013 ACR/ EULAR CRITERIA FOR CLASSIFICATION OF SYSTEMIC SCLEROSIS		
ITEM	**SUB-ITEM**	**SCORE**
Skin thickening of the fingers of both hands extending ot the MCP	-	9
Skin thickening of fingers (only count the higher score)	Puffy fingers Sclerodactyly of fingers (distal to MCP but proximal to PIP)	2 4
Fingertip lesions (only count the higher score)	Digital tip ulcers Finger pitting scars	2 3
Telengiectasias	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease (Maximum score is 2)	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III) (Maximum score is 3)	Anticentromere 3 Anti-topoisomerase I Anti-RNA polymerase III	3
Total score ≥9 means definite scleoderma		

9.8.7. SJÖGREN'S SYNDROME

"It is a multi-systemic autoimmune condition characterized by lymphocytic destruction of salivary and lacrimal glands."

QUICK FACTS: SJÖGREN'S SYNDROME	
Pathology:	**Unknown trigger → lymphocyte and plasma cell infiltration in exocrine glands → paucity of secretions**
Presentation:	**Fatigue, dry eyes, dry mouth, dry mucosae** **Extra-glandular features: arthralgias/arthritis, Raynaud's phenomenon, lymphadenopathy, interstitial pneumonitis, pulmonary hypertension, interstitial nephritis, cutaneous vasculitis, type 1 RTA, peripheral neuropathy** **Associations: other autoimmune diseases particularly RA, systemic sclerosis, SLE** **Increased risk of lymphoma, heart blocks**
Diagnosis:	**ANA, RA factor** **Anti-Ro, anti-La, anti-alpha-fodrin antibody, Labial or parotid biopsy**
Treatment:	**Ocular: ocular lubricants, topical steroids, oral pilocarpine or cevimeline** **Oral: frequent sips, oral pilocarpine or cevimeline** **Joint pains: NSAIDs, steroids, HCQ** **Extra-glandular: steroids, rituximab**

EPIDEMIOLOGY:

- Gender: Female: Male ratio = 9:1

- Age: Middle-age
- Genetics: HLA DR3, HLA-DR52

PATHOPHYSIOLOGY:
- Unknown trigger → lymphocyte and plasma cell infiltration in exocrine glands → destruction and atrophy of glands → paucity of secretions

TYPES:
- Primary: occurs alone
- Secondary: occurs with other autoimmune disorders

PRESENTATION:
- General features: fatigue
- Oral features: xerostomia (dry mouth, cotton-mouth sensation, burning, redness, blurred vision, difficulty swallowing food especially dry food and crackers, frequent use of water)
- Ocular features (keratoconjunctivits sicca): xerophthalmia (dry eyes, feeling of sand in eyes, inability to tolerate wearing contact lenses)
- Other dryness: dry vagina, nose, trachea, skin
- Extra-glandular features: arthralgias/arthritis, Raynaud's phenomenon, lymphadenopathy, interstitial pneumonitis, pulmonary hypertension, interstitial nephritis, vasculitis (usually cutaneous), type 1 renal tubular acidosis (30%), peripheral neuropathy
- Associations: rheumatoid arthritis, systemic sclerosis, SLE, polymyositis, antiphospholipid antibody syndrome, polyarteritis
- Complications:
    - Increased risk of non-Hodgkin's lymphoma, parotid tumors
    - Lymphocytic vasculitis
    - Infectious parotitis
    - Dental caries
    - Abortion, third degree heart block (in fetus of mothers with positive anti-SSA or anti-SSB antibodies)
    - Neonatal lupus

INVESTIGATIONS:
- General tests:
    - CBC: normocytic anemia, leucopenia, eosinophilia
    - ESR: raised
    - Serum proteins: raised gammaglobulins (polyclonal)
- Antibody tests:
    - ANA (MOST COMMON)
    - Anti RA factor
    - Anti-Ro (SS-A)
    - Anti-La (SS-B)
    - Anti-alpha-fodrin antibody (children)
- Tests for xerophthalmia:
    - Schirmer's test: filter paper inserted in eye and rate of wetting checked (<5 mm in 5 minutes is diagnostic)
    - Rose Bengal staining: detects damaged epithelial surfaces
- Tests for xerostomia:
    - Salivary flow
    - Dental examination
- Labial or parotid biopsy: lymphocytic infiltration and destruction of glands (DIAGNOSTIC)

MANAGEMENT:
- For ocular problems:
    - Artificial tears, lubricating ointments
    - Topical steroids

- Oral PILOCARPINE 5 mg four times daily or CEVIMELINE 30 mg three times daily to increase secretions
- Local cAMP or 0.05% cyclosporine drops

- For oral problems:
  - Frequent sips of water, oral hygiene
  - Oral PILOCARPINE or CEVIMELINE
- For joint pains: NSAIDs, steroids, HYDROXYCHLOROQUINE
- For extra-glandular features: glucocorticoids, RITUXIMAB

Table 9.21: 2002 AMERICAN-EUROPEAN CONSENSUS GROUP (AECG) CRITERIA FOR DIAGNOSIS OF SJÖGREN SYNDROME
1. Ocular symptoms: dry eyes for more than 3 months, foreign-body sensation, use of tear substitutes more than three times daily 2. Oral symptoms: dry mouth, recurrent swollen salivary glands, frequent use of liquids to aid swallowing 3. Ocular signs: Schirmer test, positive vital dye staining results 4. Oral signs: abnormal salivary scintigraphy, abnormal parotid sialography, abnormal sialometry findings (<1.5 ml in 15 minutes) 5. Positive minor salivary gland biopsy 6. Positive anti-SSA or anti-SSB antibody
Diagnosis requires any four of the above criteria including at least one criterion from criteria number 5 and 6

Table 9.22: 2012 AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR DIAGNOSIS OF SJÖGREN SYNDROME
1. Positive anti-SSA or anti-SSB antibody or RA factor and ANA titer of at least 1:320 2. Ocular staining score of at least 3 3. Presence of focal lymphocytic sialadenitis with a focus score of at least 1 focus/ 4 mm2 in labial salivary gland biopsy
Diagnosis requires any two of the above criteria

⇨ ***Most common symptom of Sjögren syndrome is dry mouth.***
⇨ ***Most common antibody seen in Sjögren syndrome is ANA (95%).***
⇨ ***Most accurate test for diagnosis of Sjögren syndrome is biopsy.***
⇨ ***Most common cause of death in Sjögren syndrome is development of non-Hodgkin's lymphoma.***

9.8.8. INFLAMMATORY MYOPATHIES

9.8.8.1. POLYMYOSITIS

"Polymyositis is a connective tissue disease characterized by inflammatory myopathy involving proximal muscles."

QUICK FACTS: POLYMYOSITIS	
Pathology:	**Suspected viral infection → T-cell mediated cytotoxic immunity against muslces**
Presentation:	**Proximal painful muscle weakness with fever, weight loss, morning stiffness** **Dysphagia, dysphonia, nasal regurgitation, aspiration** **Arthralgias, arthritis, mechanic's hands**
Diagnosis:	**Increased muscle enzymes** **ANA, myocyte specific antibodies** **MRI muscles, EMG, muscle biopsy**
Treatment:	**Steroids → if resistant immunosuppressants**

PATHOGENESIS:

- ? viral infection → T-cell mediated cytotoxic immunity against muscle antigens.

PRESENTATION:

- Proximal symmetrical weakness that develops over weeks to months and is usually painful (occasionally painless).
  - Hair, chair and stair symptoms: difficulty combing hair, rising from a seated position, difficulty climbing or descending stairs.

    - Weakness of other muscles may lead to dysphagia, dysphonia, nasal regurgitation, reflux esophagitis, neck flexors weakness, aspiration pneumonia.
    - Ocular muscles are not involved.
- Arthralgias/ arthritis
- Mechanic's hands: hyperkeratosis over fingers
- General features: fever, weight loss, morning stiffness, anorexia, fatigue.

INVESTIGATIONS:

- CBC: increased TLC and platelets
- ESR, CRP: may be increased
- Muscle enzymes: increased (e.g. creatine kinase, aldolase, LDH, AST)
- RA factor: sometimes increased
- Non-specific antinuclear antibody (ANA)
- Myositis specific antibodies (MSA): Anti tRNA synthetase antibody (e.g. anti-Jo-1 antibody), Anti signal recognition particle (anti SRP)
- MRI of muscles
- Electromyography: characteristic changes
- Muscle biopsy: dense chronic endomysial inflammation

TREATMENT:

- Steroids e.g. PREDNISONE 1 mg/kg for one 4 – 8 weeks
- In steroid resistant cases: immunosuppressants, IV IG, TNF alpha antagonists, rituximab and calcineurin inhibitors
- Physiotherapy and rehabilitation

9.8.8.2. DERMATOMYOSITIS

"Dermatomyositis is a connective tissue disease characterized by inflammatory myopathy along with characteristic dermatological changes."

QUICK FACTS: DERMATOMYOSITIS	
Pathology:	**Inflammatory myopathy with dermatological manifestations**
Presentation:	**Skin rashes on sun-exposed areas, malar rash, V-neck sign, Shawl sign, heliotrope rash, Holster's sign, Gottron's papules** **Proximal painuful muscle weakness** **Underlying malignancy**
Diagnosis:	**Increased muscle enzymes** **ANA, myocyte specific antibodies** **MRI muscles, EMG, skin or muscle biopsy**
Treatment:	**Skin: avoid sun-exposure, topical steroids, anti-malarials** **Muscle: steroids → if resistant immunosuppressants**

PRESENTATION:

- Dermatological features
    - Skin rashes on sun-exposed areas
    - Malar erythema
    - V-neck sign (violaceous erythema involving anterior chest)
    - Shawl sign (violaceous erythema involving upper back and shoulders)
    - Heliotrope rash (violaceous rash around eyes with peri-orbital edema)
    - Holster sign (violaceous rash on lateral surface of thighs and hips)
    - Gottron's papules (erythematous papules over extensor surfaces of fingers)
- Muscle weakness which is usually proximal and involves both upper and lower limbs usually painless (sometimes tender)
    - Hair, chair and stair symptoms.

    - Weakness of other muscles may lead to dysphonia, reflux esophagitis, neck flexor muscle weakness.
- Arrhythmias
- Subcutaneous calcification
- Other features: fever, arthralgia, weight loss, Raynaud's phenomenon

INVESTIGATIONS:

- CBC: increased TLC and platelets
- ESR, CRP: may be increased
- Muscle enzymes: increased (e.g. creatine kinase, aldolase, LDH, AST)
- Non-specific ANA
- Myositis specific antibodies e.g. Anti-Mi-2, Anti-Jo-1
- MRI of muscles
- Screen for malignancy
- Electromyography
- Skin or muscle biopsy
- Tests for complications/ associations e.g. malignancies

TREATMENT:

- Avoid sun-exposure
- Physiotherapy and rehabilitation
- Topical steroids or anti-malarials for skin disease
- Systemic steroids for muscles disease
- Immunosuppressants (methotrexate, mycophenolate mofetil, azathioprine, rituximab, sirolimus)
- IV immunoglobulins
- Diltiazem or colchicine for calcinosis

9.8.8.3. INCLUSION BODY MYOSITIS

"It is an inflammatory myopathy with proximal and distal muscle involvement and characteristic cytoplasmic vacuoles and inclusions."

It presents as asymmetrical proximal and distal muscle weakness along with dysphagia.

⇨ ***Inclusion body myositis is the most common inflammatory myopathy in elderly patients.***

9.8.9. MIXED CONNECTIVE TISSUE DISEASE (MCTD)

"It is a connective tissue disease with overlapping features of SLE, scleroderma and myositis characterized by presence of anti-U1-ribonucleoprotein."

QUICK FACTS: MIXED CONNECTIVE TISSUE DSIEASE	
Pathology:	**Hyper-reactive B-lymphocytes → activate T-cells → apoptotic modification**
Presentation:	**Raynaud's phenomenon, arthralgias/ arthritis, esophageal motility, acrosclerosis, pulmonary fibrosis, pulmonary hypertension, myositis, serositis**
Diagnosis:	**Speckled ANA, anti-U1-RNP, anti-U1-70-snNRP**
Treatment:	**Steroids, immunosuppressants**

EPIDEMIOLOGY:

- Age: 15 – 25 years
- Female: male ratio =3:1

PATHOGENESIS:

- Hyper-reactive B lymphocytes → T-lymphocyte activation → apoptotic modification → immune response

FEATURES:

- Raynaud's phenomenon
- Arthralgia/ arthritis
- Esophageal dysmotility
- Acroslcerosis
- Pulmonary fibrosis
- Pulmonary hypertension
- Myositis
- Serositis (pleuritis/ pericarditis)

INVESTIGATIONS:

- Antinuclear antibody (speckled)
- Antibodies against U1-ribonucleoprotein (anti-U1-RNP)
- Antibodies against U1-70 kd small nuclear ribonucleoprotein (anti-U1-70-snNRP)
- Others: RA factor, antiphospholipid antibodies

MANAGEMENT:

- Steroids
- Immunosuppressants

9.8.10. RELAPSING POLYCHONDRITIS

"It is a severe, episodic and progressive inflammation of cartilaginous structures."

QUICK FACTS: RELAPSING POLYCHONDRITIS	
Pathology:	**Autoimmune destruction of cartilage and collagen**
Presentation:	**Red, swollen and painful cartilage → deformities** **Peripheral arthropathy** **Others: fever, episcleritis, uveitis, deafness, aortic insufficiency** **Associated autoimmune diseases**
Diagnosis:	**Clinical diagnosis**
Treatment:	**Steroids; Steroid-sparing agents: dapsone or methotrexate**

- It mostly involves ears, nose, trachea and larynx however may also involve eyes, cardiovascular system, skin and CNS.

PATHOGENESIS:
- Autoimmune destruction of cartilage and collagen leading to chondrolysis.

FEATURES:
- During attack the cartilage is red, swollen and painful and progressively atrophies leading to deformities.
- Peripheral joint involvement includes a migratory, asymmetric and seronegative arthropathy affecting both large and small joints and costo-chondral junctions.
- Other features include fever, episcleritis, uveitis, deafness, aortic insufficiency, glomerulonephritis.

ASSOCIATIONS:
- SLE, RA, Hashimoto thyroiditis, multiple myeloma, myelodysplastic syndrome.

COMPLICATIONS:
- Joint deformities; tracheomalacia; saddle-nose deformity; voice changes.

TREATMENT:
- Steroids: PREDNISONE 0.5 – 1 mg/kg/day PO.
- Steroid-sparing agents: DAPSONE 100 – 200 mg/day PO or METHOTREXATE 7.5 – 20 mg/week PO.

9.9. SERONEGATIVE SPONDYLOARTHROPATHIES

9.9.1. ANKYLOSING SPONDYLITIS

"It is a chronic multi-systemic inflammatory seronegative spondyloarthropathy which primarily involves axial joints and sacroiliac joints and progressively leads to stiffening of spine."

QUICK FACTS: ANKYLOSING SPONDYLITIS	
Pathology:	**Lymphocytic and monocytic inflammation → subchondral granulation tissue → erosion**
Presentation:	**Low back pain, restriction of spinal movements** **Restrictive lung disease** **Transient acute arthritis, enthesopathy, anterior uveitis**
Diagnosis:	**MRI SI joints, X-rays, HLA-B27**
Treatment:	**NSAIDs → TNF inhibitors in NSAID refractory cases** **Sulfasalazine** **Short term steroids**

EPIDEMIOLOGY:
- Males > Females

- Age usually <40 years.

PATHOGENESIS:

- Inflammation involving CD4+ and CD8+ lymphocytes and macrophages → subchondral granulation tissue → erodes into joints → fibrocartilage formation → ossification.

CLINICAL PRESENTATION:

- Low back pain: gradual onset; chronic; may radiate to buttocks; associated with morning stiffness; usually worse in morning and after rest; improves after exercise.
- Symptoms slowly progress upwards and the spinal movements become restricted. Lumbar curvature is flattened and thoracic curvature is exaggerated.
- Dyspnea due to restrictive lung disease caused by fusion of costo-vertebral joints.
- Transient acute arthritis of peripheral joints.
- Enthesopathy: Achilles tendonitis, plantar fasciitis, sausage fingers or toes.
- Anterior uveitis
- Heart involvement: AV conduction defects, aortic regurgitation

Table 9.23: EXTRA-ARTICULAR MANIFESTATIONS OF ANKYLOSING SPONDYLITIS
• Anterior uveits • Atlanto-axial subluxation • AV blocks • Aortic regurgition • Apical/ upper lobe fibrosis • Autoimmune disease of bowel (IBD) • Amyloidosis of kidney • Achilles tendonitis • Cauda equine syndrome • Osteoporosis

INVESTIGATIONS:

- ESR high
- RA factor negative
- Anti-CCP negative
- Anemia may be present.
- HLA B27 positive (90%)
- X-ray spine
- MRI

RADIOLOGIC CHANGES:

- Bilateral and symmetric sacroileitis = blurred subchondral plate, irregular erosions of margins.
- Romanus lesion/ Shiny corner sign = sclerosis of superior and inferior margins of vertebral bodies at sites of attachment of annulus fibrosus
- Erosions of superior and inferior margins of vertebral bodies → squaring of vertebrae
- Bamboo spine = fusion of vertebral bodies by vertical bridging syndesmophytes formed by ossification of annulus fibrosus annulus fibrosus and calcification of anterior and lateral spinal ligaments.
- Non-erosive, asymmetric changes in involved peripheral joints

TREATMENT:

- NSAIDs are the first line treatment.
- TNF inhibitors for NSAID-refractory disease.
    - ETANERCEPT 50 mg SC once a week.
    - ADALIMUBAB 40 mg SC every other week.
    - INFLIXIMAB 5 mg/kg IV infusion every other month.
- Sulfasalazine 1000 mg PO BID can be used for peripheral arthritis or with co-existent IBD.
- Corticosteroids should only be used for short-term management.

- Swimming is the best exercise for these patients.

9.9.2. PSORIATIC ARTHRITIS

"It is a sero-negative arthritis seen in association with psoriasis."

QUICK FACTS: PSORIATIC ARTHRITIS	
Pathology:	**IL or TNF mediated arthritis in psoriasis**
Presentation:	**Any of 5 patterns: symmetric polyarthritis, asymmetrical oligoarthritis, DIP joint predominant arthritis, spondylitis with or without sacroileitis and arthritis mutilans** **Psoriatic skin lesions and nail changes** **Enthesopathy and dactylitis**
Diagnosis:	**Clinical diagnosis**
Treatment:	**NSAIDs → Disease modifying agents like methotrexate, sulfasalazine, cyclosporine, leflunomide** **TNF inhibitors, phosphodiesterase-4 inhibitors, IL-12/23 inhibitors**

CLINICAL PRESENTATION:

There are 5 patterns of joint involvement:

1. Symmetric polyarthritis like rheumatoid arthritis (most common) – 25%
2. Asymmetrical oligoarticular arthritis – 40%
3. DIP joint predominant arthritis
4. Spondylitis with or without sacroiliitis like ankylosing arthritis (50% HLA-B27 positive)
5. Arthritis mutilans (severe deformities plus osteolysis)

- Skin lesions occur before arthritis in 80% of patients. In 20% of patients arthritis occurs before or concomitantly along with skin lesions. Lesions may have cleared when arthritis appears or may be hidden.
- Enthesopathy: Achilles tendonitis, plantar fasciitis, dactylitis (sausage-fingers).
- Nail-changes: pitting, onycholysis, leukonychia, subungual hyperkeratosis, transverse ridging, Beau lines, etc.

Table 9.24: HIDDEN SITES OF PSORIASIS

- Scalp (confused with dandruff)
- Inter-gluteal cleft
- Perineum and genitals
- Umbilicus
- Armpits
- Under-surface of breasts

Table 9.25: CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS - CASPAR
(≥ 3 points diagnostic)

Features	Score
Current psoriasis	2
History of psoriasis	1
Family history of psoriasis	1
Dactylitis	1
Juxta-articular new-bone formation	1
Negative RA factor	1
Nail dystrophy	1

INVESTIGATIONS:

- ESR is high.
- RA factor is not raised.
- Uric acid levels are high.
- Synovial fluid is inflammatory in nature.
- Iron profile may show iron deficiency anemia.

IMAGING:

- Erosions of bone
- Irregular destruction of joint and bone → sharpened pencil appearance
- Pencil-in-cup deformity
- Unilateral or asymmetric sacroiliitis

TREATMENT:

- NSAIDS
- Disease modifying agents: include METHOTREXATE, SULFASALAZINE, CYCLOSPORINE and LEFLUNOMIDE.
- METHOTREXATE 7.5 – 20 mg PO once weekly for patients not responding to NSAIDS.
- Consider methotrexate, retinoic-acid derivatives and psoralen plus UV light
- TNF inhibitors for Methotrexate-refractory cases e.g. CERTOLIZUMAB
    - ***Screen all patients for TB, HIV, HBV and HCV before starting anti-TNF medicines.***
- Corticosteroids are ineffective however can be used locally as adjunctive treatment.
    - ***Anti-malarials can precipitate psoriasis.***
- Phosphodiesterase-4 inhibitors: APREMILAST
- Interleukin-12/23 inhibitors: USTEKINUMAB

➢ **Read PSORIASIS for further information.**

9.9.3. REACTIVE ARTHRITIS

"It is an asymmetric inflammatory autoimmune oligoarthritis which follows acute infections (particularly genitourinary or gastrointestinal infections)."

QUICK FACTS: REACTIVE ARTHRITIS	
Pathology:	**Bacterial antigens presented to HLA-B27 → inflammatory reaction**
Presentation:	**Recent history of GIT or UGT infection** **Arthritis: asymmetrical oligo-arthritis or mono-arthritis** **Genitourinary: urethritis, prostatitis, cervicitis, salpingitis** **Ocular: conjunctivitis, uveitis, keratitis** **Mucocutaneous, peri-articular and other features**
Diagnosis:	**Clinical diagnosis with negative ANA or RA factor**
Treatment:	**NSAIDS → if fail then give steroids or sulfasalazine, immunosuppressants or anti-TNF agents**

EPIDEMIOLOGY:

- Male:Female ratio = 1:1
- Age: 20 – 50 years
- HLA-B27 positive patients (85%)

ASSOCIATED ORGANISMS:

- GI infections: Salmonella, Shigella, Campylobacter, Yersinia, Clostridium
- GU infections: Chlamydia trachomatis
- May be associated with HIV

PATHOPHYSIOLOGY:

- Bacterial lipopolysaccharides and nucleic acids are presented to HLA-B27 → inflammatory reaction

PRESENTATION:

- Recent history of gastrointestinal or genitourinary infection (1 – 4 week ago).
- Asymmetric arthritis: acute asymmetric inflammatory oligoarthritis which progresses sequentially from one joint to other. It mostly involves lower limbs and may involve sacroiliac joints.
- Genitourinary features: non-gonococcal urethritis, prostatitis, cervicitis, salpingitis

- Ocular features: conjunctivitis, uveitis, keratitis, optic neuritis
- Mucocutaneous lesions: circinate balanitis, oral mucosal lesions, keratoderma blennorrhagica
- Peri-articular features: enthesitis, dactylitis, plantar fasciitis, Achilles tendonitis
- General features: fatigue, malaise, weight loss, fever
- Others: pleuropericarditis, aortitis, aortic regurgitation, neurological manifestations

INVESTIGATIONS:
- Negative RA factor and ANA
- CBC: anemia, leukocytosis,
- CRP and ESR: raised
- Synovial fluid analysis: inflammatory
- X-rays: may show erosions with periosteal reaction
- Workup of underlying cause

MANAGEMENT:
- First-line: NSAIDs e.g. INDOMETHACIN 25 – 50 mg PO thrice daily
- Second-line:
    - Steroids (systemic or intra-articular). These are also given in uveitis.
    - SULFASALAZINE 1 g PO two to three times daily
    - Immunosuppressants e.g. AZATHIOPRINE 1 – 2 mg/kg/day, METHOTREXATE 7.5 – 15 mg/week
    - Anti-TNF agents (severe cases)
- Antibiotics (no role) – tetracyclines in case of Chlamydia e.g. DOXYCYCLINE 100 mg BD twice for three months

⇨ ***It is the most common cause of inflammatory oligo- or poly-arthritis in young men.***
⇨ ***Classic triad of reactive arthritis: conjunctivitis + non-infectious urethritis + arthritis (Can't See + Can't Pee + Can't climb a tree)***
⇨ ***Classic tetrad of reactive arthritis: triad + muco-cutaneous lesions***

- Reiter's arthritis is a subset of reactive arthritis and the name is no longer used. It presents with the classic triad.
- Undifferentiated spondyloarthropathy is presence of reactive arthritis without classical features and absence of previous infection.

9.9.4. ARTHRITIS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASES

Aka enteropathic arthritis

"It is arthritis seen in patients with inflammatory bowel disease."

QUICK FACTS: ARTHRITIS ASSOCIATED WITH IBD	
Pathology:	**Cytokines or antigen antibody complexes in IBD → arthritis**
Presentation:	**Peripheral arthritis correlating with disease activity** **Axial arthritis/ spondylitis not correlating with disease activity**
Diagnosis:	**Clinical diagnosis**
Treatment:	**NSAIDS, intra-articular steroids, DMARDs, TNF inhibitors**

- It is seen in 10% of patients with ulcerative colitis and 20% of patients with Crohn's disease.

TYPES:
- Peripheral arthritis:
    - It mainly affects knees, ankles and hips.
    - It is non-erosive and non-deforming arthritis.
    - It is associated with HLA-DR103.
    - It may oligo-articular or polyarticular.
    - It may involve wrists and small joitns of hands.
    - It occurs concurrently during flares of IBD.
    - Oligoarticular arthritis improves with treatment of IBD and is cured by total colectomy.

- Axial arthritis/ spondylitis:
    - Sacroileitis (16%) and ankylosing arthritis (6%).
    - It is associated with HLA-B27.
    - Arthritis does not correlate with activity of IBD.

INVESTIGATIONS:

- None specific

MANAGEMENT:

- NSAIDs (better be avoided)
- Intra-articular steroids
- DMARDs e.g. METHOTREXATE
- TNF inhibitors e.g. INFLIXIMAB, ADALIMUBAB

9.10. NEUROPATHIC JOINT DISEASE

Aka Charcot joints/ Charcot arthropathy

"It is a destructive and deforming disease of joints caused by neuropathy."

Table 9.26: CAUSES OF CHARCOT JOINTS
• Diabetes (most common) • Syringomyelia • Meningomyelocoele • Syphilis • Chronic alcoholism • Leprosy • Spinal cord injury

9.11. POLYMYALGIA RHEUMATICA (PMR)

"It is a chronic inflammatory condition of musculoskeletal system causing widespread proximal aching and stiffness in elderly patients."

QUICK FACTS: POLYMYALGIA RHEUMATICA	
Pathology:	**Unknown trigger → monocytic inflammation of girdle joints along with their bursae**
Presentation:	**Pain, tenderness and morning stiffness in shoulders, pelvic girdle and proximal limb muscles**
Diagnosis:	**Clinical diagnosis supported by increased ESR and IL-6**
Treatment:	**Response to steroid trial** **Prednisone 15 mg daily**

EPIDEMIOLOGY:

- Age: >50 years (usually 70 years)
- Gender: females > males
- Genetics: HLA DR4

PATHOPHYSIOLOGY:

- Unknown trigger → autoimmune monocyte-mediated inflammation of shoulder and hip joints along with their bursae (? Non-erosive synovitis and tenosynovitis)

PRESENTATION:

- Pain and tenderness in both shoulders, pelvic girdle and proximal limb muscles (muscular pain is actually referred pain) → difficulty rising from chair
- Onset is usually sub-acute. Disease is self-limiting in 1 – 2 years.

- Absence of true muscle weakness
- Morning stiffness
- Others: carpal tunnel syndrome, peripheral arthritis, fatigue, low-grade fever
- Associations: giant cell arteritis

INVESTIGATIONS:

- CRP: increased
- ESR: increased (usually >40 mm/hour)
- Alkaline phosphatase: increased in 30%
- Interleukin-6: high
- ANA, RA factor: normal
- CPK and aldolase: normal
- Rule out similar conditions e.g. RA, hypothyroidism, hypovitaminosis D, liver disease, other autoimmune conditions

MANAGEMENT:

- PREDNISOLONE 15 mg (12.5 - 25) PO daily
- If responds then decrease steroid dose by 1 mg per month very slowly
- If no response within one week, consider alternative diagnoses
- NSAIDs are of no benefit

Table 9.27: 2012 EULAR/ ACR CRITERIA FOR DIAGNOSIS OF POLYMYALGIA RHEUMATICA

Required criteria: age ≥50 years, bilateral shoulder aches, abnormal CRP and/or ESR		
	Points without ultrasound findings	**Points with ultrasound findings**
Morning stiffness >45 minutes	2	2
Hip pain or limited range of motion	1	1
Absence of RA factor or anti CCP	2	2
Absence of other joint involvement	1	1
Ultrasound findings: At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis	N/A	1
Ultrasound findings: Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis	N/A	1
Diagnostic of PMR likely if: ≥4 without ultrasound findings ≥5 with ultrasound findings		

9.12. VASCULITIS SYNDROMES

Table 9.28: CLASSIFICATION OF PRIMARY VASCULITIS SYNDROMES ACCORDING TO INVOLVED DOMINANT VESSEL TYPE	
Large arteries	Giant cell arteritis Takayasu's arteritis
Medium arteries	Polyarteritis nodosa Kawasaki disease
Medium arteries and small vessels	**ANCA-associated:** Wegener's granulomatosis Churg-strauss syndrome Microscopic polyangiitis **Immune-complex vasculitis:** Cryoglobulinemia Henoch-Schönlein purpura Hypocomplementemicurticarial vasculitis Cutaneous leukocytoclastic vasculitis Good-pasture syndrome
Variable vessels	Behçet disease Cogan syndrome

Table 9.29: SECONDARY CAUSES OF VASCULITIS
• Connective tissue disorders: rheumatoid arthritis, SLE, Sjogren syndrome, vasculitis associated with IBD, sarcoidosis • Infections: infective endocarditis, syphilis, tuberculosis, rickettsia, leprosy, HIV, parvovirus B19, VZV, CMV, HSV, Hepatitis B associated polyarteritis nodosa, Hepatitis C associated cryoglobulinemia • Neoplastic causes: myeloproliferative and lymphoproliferative diseases • Drugs e.g. beta-lactams

Table 9.30: ANCA-ASSOCIATED VASCULITIS
• Wegener's granulomatosis • Microscopic polyangiitis • Churg-Strauss syndrome • Renal limited vasculitis

⇨ ***Small vessel vasculitides typically present as pulmo-renal syndromes with purpura and neuropathy.***

9.12.1. GIANT CELL ARTERITIS (GCA)

Aka Temporal arteritis, Horton disease

"It is a predominantly medium- to large-vessel vasculitis characterized by granulomatous pan-arteritis."

QUICK FACTS: GIANT CELL ARTERITIS	
Pathology:	**Idiopathic granulomatous vasculitis of large and medium sized vessels**
Presentation:	**Temporal artery: unilateral headache, temporal tenderness, absent temporal pulse** **Ophthalmic artery: amaurosis fugax, blindness** **Aorta: aneurysms, dissection** **Systemic features: fever, malaise, fatigue,** **Associated polymyalgia rheumatica**
Diagnosis:	**Clinical diagnosis supported by raised ESR** **Temporal artery biopsy**
Treatment:	**High dose steroids**

EPIDEMIOLOGY:

- Gender: Male: Female ratio = 1:2
- Age: >50 years

PATHOPHYSIOLOGY:

- Unknown cause →granulomatous inflammation in blood vessels→ mural hyperplasia

PRESENTATION:

- Due to involvement of different vessels:
  - Carotid arteries (especially extra-cranial branches):
    - Temporal arteries (MOST COMMON): usually new-onset unilateral headache, tender/palpable temporal artery, absent temporal pulse
    - Subclavian bruits
    - Ophthalmic arteries: visual impairment due to optic neuritis or amaurosis fugax (may lead to blindness if not treated early)
  - Aorta: increased risk of aortic aneurysm and aortic dissection
  - Other arteries: Raynaud's phenomenon, claudication, jaw claudication (pain in jaw or tongue on chewing)
- General features: low-grade fever, malaise, fatigue, weight loss, palpable nodules
- Respiratory symptoms: dry cough
- Associations: polymyalgia rheumatica (40%)

INVESTIGATIONS:

- ESR: usually raised, may be normal
- CBC: normocytic normochromic anemia
- Temporal arterial biopsy: (90% sensitive and diagnostic but negative biopsy does not rule out diagnosis as lesions can be segmental)

MANAGEMENT:

- High dose steroids e.g. PREDNISONE 1 mg/kg
  - Start immediately on suspicion to prevent vision loss which can be permanent
  - If diagnosis is confirmed then continue treatment for 4 weeks, then taper gradually to maintenance dose. Continue maintenance dose for 2 – 3 years.
  - Monitor with clinical response and ESR.
- Disease is self-limiting but vision loss may be permanent.

⇨ ***Giant cell arteritis is the most common vasculitis in adults.***

⇨ ***Temporal arteries are the most frequently affected arteries in giant cell arteritis.***

⇨ ***Most common presentation of giant cell arteritis is a new-onset headache.***

9.12.2. TAKAYASU'S ARTERITIS

Aka pulseless disease, aortic arch syndrome

"It is a granulomatous vasculitis of large vessels including aorta and its major branches."

QUICK FACTS: TAKAYASU'S ARTERITIS	
Pathology:	**Idiopathic granulomatous vasculitis of large and medium sized vessels → vascular narrowing or aneurysm**
Presentation:	**Systemic phase: headache, joint pain, fever, malaise** **Occlusive phase: findings according to involved blood vessel e.g. common carotid, subclavian, renal, aortic arch, branches of aorta, etc.** **Burned out phase: fibrosis**
Diagnosis:	**CT, MR or invasive angiogram**
Treatment:	**Steroids, immunosuppressants** **Angioplasty or bypass procedures**

- It mostly occurs in women of child-bearing age (<50 years of age). It is 9 times more common in females.

PATHOGENESIS:

- Unknown etiology → granulomatous vasculitis of large and medium sized vessels → intimal fibrsosis → vascular narrowing (cork-screw configuration) or aneurysm

Table 9.31: AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA FOR TAKAYASU'S ARTERITIS (Any 3 of 6 criteria)
1. Age <40 years 2. Claudication of extremities 3. Decreased pulsation in one/ both brachial arteries 4. Difference of at least 10 mmHg of systolic pressure in between arms 5. Bruit over one/ both subclavian arteries/ abdominal aorta 6. Arteriographic narrowing/ occlusion of entire abdominal aorta, its primary branches or large arteries of both upper and lower limbs

PRESENTATION:

- Systemic phase (characterized by active inflammation): headache, joint pains, fever, malaise, weight loss, tenderness over affected arteries
- Occlusive phase:
    - Findings depend on involved areas
    - Common carotid: visual changes, headache, stroke
    - Subclavian: arm claudication, Raynaud's phenomenon, difference in blood pressure between limbs
    - Renal: HTN, renal artery stenosis, renal failure
    - Aortic arch/ root: aortic regurgitation, CHF
    - Abdominal aorta or abdominal visceral branches: abdominal pain, nausea
    - Coronary: ischemic heart disease
    - Pulmonary: hemoptysis, pulmonary embolism
    - Iliac: leg claudication
    - Dermatological features: erythema nodosum
- Burned-out phase:
    - Fibrosis occurs and disease undergoes remission

INVESTIGATIONS:

- CBC: normocytic anemia
- ESR: high
- CT or MR angiogram
- Invasive angiogram

MANAGEMENT:

- Steroids e.g. PREDNISONE 1 mg/kg/day tapered over several days
- Steroid-sparing agents for long-treatment e.g. METHOTREXATE, AZATHIOPRINE, CYCLOPHOSPHAMIDE
- Low dose ASPIRIN
- Angioplasty for renal artery stenosis
- Vascular bypass procedures

9.12.3. POLYARTERITIS NODOSA (PAN)

"It is a systemic necrotizing vasculitis involving medium-sized vessels primarily of nervous system and GI tract with characteristic arterial nodule and micro-aneurysm formation."

QUICK FACTS: POLYARTERITIS NODOSA	
Pathology:	**Unknown trigger → mononuclear and neutrophilic infiltration of blood vessels → fibrinoid necrosis and intimal proliferation**
Presentation:	**Fever, weakness and other constitutional features** **Purpura, livedo reticularis and ulceration especially on legs** **Ischemia or infarction of areas supplied by involved vessels: peripheral neuropathy, CVA, mesenteric ischemia, renal infarction, MI, testicular infarction**
Diagnosis:	**Biopsy of involved tissue** **Abdominal angiography**
Treatment:	**Steroids → cyclophosphamide (if severe)** **Antivirals in hepatitis B or C**

EPIDEMIOLOGY:

- Age: usually 40 – 50 years
- Gender: male to female ratio is 2:1

PATHOPHYSIOLOGY:

- Unknown trigger → mononuclear infiltration of all layers of blood vessels → followed by neutrophilic infiltration → fibrinoid necrosis → intimal proliferation → ischemia, thrombosis, infarction and aneurysm formation.
- It is either idiopathic or associated with HBV, HIV, drug reactions.

PRESENTATION:

- Early features: fever, weakness, weight loss, myalgias, arthralgias, abdominal pain
- Neurological features: peripheral neuropathy (mononeuritis multiplex, polyneuropathy), CNS lesions (ischemia, arteritis, hemorrhage)
- Dermatological features (usually in legs): purpura, livedo reticularis, ulcers, nodules, gangrene
- Renal features: renal arterial vasculitis (proteinuria, renal failure, hypertension, renal infarcts)
- Gastrointestinal features: abdominal pain, GI bleeding
- Cardiac features: vasculitis (usually asymptomatic), myocardial infarctions, heart failure
- Others: scleritis, testicular infarction, psychosis, depression
- Associations: HBV, HCV, HIV, drug reactions

INVESTIGATIONS:

- ESR: raised
- p-ANCA: may be present
- Stool for occult blood: may be positive
- Urine analysis: proteinuria
- Biopsy of involved tissue (skin, nerve or muscle): focal necrotizing arteritis of generally mixed cellular infiltrate
- Abdominal angiography: aneurysms (renal, hepatic or mesenteric)

MANAGEMENT:

- Prognosis: poor and improves little with treatment
- Treatment:
    - Steroids
    - If severe: cyclophosphamide
    - Add antivirals in case of hepatitis B or C related PAN

Table 9.32: 1990 ACR CRITERIA DIAGNOSTIC CRITERIA FOR POLYARTERITIS NODOSA *Mnemonic: Weight Lifters Test Muscles & Nerves, Become Hyper And Rent Biopics.*	
W	Weight loss of >kg since illness
L	Livedo reticularis
T	Testicular pain or tenderness
M	Myalgias, weakness or leg tenderness
N	Neurological: mononeuropathy or polyneuropathy
B	Presence of hepatitis B surface antigen or antibody in serum
H	Hypertension
A	Arteriogram showing aneurysms or occlusion of the visceral arteries
R	Renal: elevated BUN or creatinine unrelated to dehydration or obstruction
B	Biopsy of small or medium-sized artery containing granulocytes
Diagnosis requires 3 out of 10 criteria.	

9.12.4. KAWASAKI'S DISEASE

"It is an acute febrile vasculitis in children with characteristic rash, mucosal and ocular involvement."

QUICK FACTS: KAWASAKI'S DISEASE	
Pathology:	**Acute febrile vasculitis in children**
Presentation:	**Fever** **Rash: polymorphous, erythema, edema of extremities followed by desquamation** **Mucosal features: erythema/ fissuring of lips, strawberry tongue** **Others: lymphadenopathy, coronary aneurysms, coronary vasculitis, involvement of liver, kidney or GI tract**
Diagnosis:	**Clinical diagnosis + raised CRP and ESR**
Treatment:	**Steroids, IVIG, immunosuppressants, anti-platelets, anti-coagulants**

PRESENTATION:

- Fever
- Rash (polymorphous)
- Ocular features: bulbar conjunctivitis, uveitis
- Oropharyngeal changes: erythema and fissuring of lips, strawberry tongue
- Lymphadenopathy
- Cardiac involvement: coronary aneurysms, coronary vasuclitis, myocarditis, pericarditis
- Vasculitic visceral involvement: liver, kidney, GI tract
- Erythema, edema of extremities followed by desquamation, absence of vesicles

INVESTIGATIONS:

- ESR, CRP: raised

MANAGEMENT:

- Steroids, IVIG, immunosuppressants, antiplatelets, anticoagulation

⇨ ***Kawasaki disease is the most common cause of acquired heart disease in children.***

9.12.5. GRANULOMATOSIS WITH POLYANGIITIS (GPA)

Aka Wegener's granulomatosis

"It is a granulomatous necrotizing small-to-medium vessel vasculitis with characteristic involvement of kidneys, upper respiratory tract and lungs."

QUICK FACTS: GRANULOMATOSIS WITH POLYANGIITIS	
Pathology:	**Unknown trigger → necrotizing granulomatous inflammation of small- and medium-sized vessels → pauci-immune vasculitis**
Presentation:	**Constitutional features: Fever, weight loss, night sweats, fatigue, arthralgias, arthritis, myalgias** **Upper respiratory features: sinusitis, rhinitis, otitis media** **Lower respiratory features: pulmonary infiltrates, diffuse alveolar hemorrhages, atelectasis** **Renal features: crescentic necrotizing glomerulonephritis** **Others: conjunctivitis, scleritis, uveitis, retro-orbital granulomatous masses, palpable purpura**
Diagnosis:	**C-ANCA and open lung biopsy**
Treatment:	**Induction: cyclophosphamide or rituximab + high-dose steroids** **Maintenance: steroids**

EPIDEMIOLOGY:

- Age: any age (usually 35 – 55 years)
- Gender: male:female ratio = 1.5:1

PATHOPHYSIOLOGY:

- Environmental exposures → necrotizing granulomatous inflammation in walls of small- and medium-sized vessels → pauci-immune vasculitis

PRESENTATION:

- General features: fever, weight loss, night sweats, fatigue
- Oral ulcers (sometimes painful), strawberry gingival hyperplasia
- Upper respiratory tract: sinusitis (purulent or bloody), rhinitis, saddle-nose deformity, recurrent serous otitis media and hearing loss, subglottic or tracheal stenosis
- Lower respiratory tract: cough, hemoptysis, dyspnea, pulmonary infiltrates, diffuse alveolar hemorrhages, atelectasis
- Renal: crescentic necrotizing glomerulonephritis (may lead to rapidly progressive renal failure)
- Ocular features: conjunctivitis, scleritis, episcleritis, uveitis, retro-orbital granulomatous masses
- Cutaneous features: palpable purpura, skin ulcers, petechiae, vesicles, livedo reticularis
- Others: arthralgias, arthritis, myalgias, mononeuritis multiplex, sensorimotor polyneuropathy

INVESTIGATIONS:

- ESR: elevated
- CBC: normocytic normochromic anemia, thrombocytopenia
- Chest x-ray: nodules (most common) or infiltrates
- Urine detailed report: hematuria, proteinuria
- Renal function tests: abnormal creatinine
- Cytoplasmic anti-nuclear cytoplasmic antibody or c-ANCA (anti-proteinase III): positive in 90%
- P-ANCA in some patients
- Open lung biopsy (CONFIRMATORY)

MANAGEMENT:

- Most patients die within one year of diagnosis.
- Treatment:
    - To induce remission:
        - CYCLOPHOSPHAMIDE + high-dose steroids

        - RITUXIMAB + high-dose steroids
        - METHOTREXATE + high-dose steroids (in mild disease)
    - Maintenance: steroids
- Trimethoprim-sulfamethoxazole (controversial role in upper respiratory tract limited disease)
- Renal transplant in end-stage renal disease.
- It tends to relapse.

⇨ ***Classical triad of organ involvement in Wegener's granulomatosis: upper respiratory tract + lower respiratory tract + kidney***

⇨ ***Wegener's granulomatosis is differentiated from polyarteritis nodosa by: presence of pulmonary findings.***

⇨ ***Wegener's granulomatosis is differentiated from EGPA by: absence of eosinophilia and asthma.***

Table 9.33: 1990 ACR DIAGNOSTIC CRITERIA FOR GRANULOMATOSIS WITH POLYANGIITIS *Mnemonic: GMUX*	
G	Granulomatous inflammation on biopsy Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)
M	Mucosal inflammation: nasal or oral inflammation Development of painful or painless oral ulcers or purulent or bloody nasal discharge
U	Urinary sediment Microhematuria (>5 red blood cells per high power field) or red cell casts in urine sediment
X	X-ray: Abnormal chest radiograph Chest radiograph showing the presence of nodules, fixed infiltrates or cavities
Diagnosis requires 2 out of 4 criteria.	

9.12.6. EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Aka Churg-Strauss Syndrome, allergic granulomatosis with angiitis

"It is a systemic eosinophilic-rich necrotizing granulomatous vasculitis affecting small-to-medium-sized vessels associated with severe asthma."

QUICK FACTS: EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS	
Pathology:	**Unknown environmental factor → infiltration of eosinophils in skin, different tissues and around blood vessels**
Presentation:	**Stages of asthma, eosinophilia and vasculitis** **General: fever, weight loss, fatigue** **Pulmonary infiltrates, asthma or alveolar hemorrhages, allergic rhinitis and sinusitis, nasal polyps,** **Mononeuritis multiplex, leucocytoclastic angiitis, glomerulonephritis, hypertension, myocarditis**
Diagnosis:	**Eosinophilia, increased ESR and fibrinogen** **p-ANCA, chest imaging** **Lung biopsy**
Treatment:	**Steroids → immunosuppressants**

EPIDEMIOLOGY:

- Age: any age (usually 48 years)
- Gender: equal in males and females

PATHOPHYSIOLOGY:

- Unknown environmental factor → infiltration of tissues (skin, cardiovascular system, kidneys, peripheral nerves, GI tract) with eosinophils and around vessels (including small- and medium-sized arteries, capillaries, veins and venules) → granulomatous reaction

Three phases of disease: asthma → eosinophilia → vasculitis

PRESENTATION:

- General features: fever, weight loss, fatigue, anorexia
- Pulmonary features (most common): dyspnea, asthma, pulmonary infiltrates, alveolar hemorrhages
- Neurologic features: mononeuritis multiplex
- Upper respiratory features: allergic rhinitis and sinusitis, nasal polyps
- Dermatological features: subcutaneous nodules, leukocytoclastic angiitis with palpable purpura
- Cardiac features: myocardial infarction, myocarditis, heart failure
- Gastrointestinal features: vasculitic lesions, splenic granulomas
- Renal features: glomerulonephritis, hypertension
- Others: arthralgias, stroke

INVESTIGATIONS:

- CBC: eosinophilia (usually >1000 cells/μL)
- Inflammatory markers: ESR, fibrinogen raised
- Perinuclear anti-nuclear cytoplasmic antibody or p-ANCA (anti-myeloperoxidase): positive in about 50%
- Lung biopsy: small necrotizing granulomas with central eosinophilic core, necrotizing vasculitis of small arteries and venules
- Imaging of chest: reveals transient infiltrates
- Rule out toxocariasis, HIV and aspergillosis

MANAGEMENT:

- Prognosis is poor (5-year survival 25%)
- Steroids:
  - 40 – 60 mg/day of PREDNISOLONE
  - Intravenous METHYLPREDNISOLONE if severe presentation
- Immunosuppressants e.g. azathioprine, cyclophosphamide, mycophenolate, methotrexate

Table 9.34: DIAGNOSTIC CRITERIA FOR CHURG-STRAUSS SYNDROME (AS PER 1990 ACR AND 1994 CHAPEL HILL CRITERIA)

Mnemonic: Ash's New Singing is Vastly Popular in Europe

A	Asthma
N	Neurological involvement = mononeuritis multiplex, polyneuropathy
S	Sinusitis = Paranasal sinusitis
V	Vasculitis = histological proof of vasculitis with extravascular eosinophils
P	Pulmonary infiltrates (may be transient)
E	Eosinophilia (>10% eosinophils in peripheral blood)
Diagnosis requires 4 out of 10 criteria.	

⇨ ***EGPA differs from PAN by presence of granulomas and eosinophils.***

9.12.7. MICROSCOPIC POLYANGIITIS (MPA)

"It is a non-granulomatous pauci-immune necrotizingvasculitis of small vesssels."

QUICK FACTS: MICROSCOPIC POLYANGIITIS	
Pathology:	**Unknown trigger → ANCA antibodies → small vessel granulomatous vasculitis**
Presentation:	**Renal: glomerulonephritis, renal failure** **Constitutional: weight loss, fever, fatigue, malaise, myalgias** **Dermatological: palpable purpura** **Neurological: mononeuritis multiplex, seizures**
Diagnosis:	**p-ANCA (80%) and c-ANCA (40%)** **Chest x-ray** **Skin biopsy, open-lung biopsy, renal biopsy**
Treatment:	**Steroids + rituximab or cyclophosphamide**

EPIDEMIOLOGY:

- Age: usually middle-aged
- Gender: equal distribution

PATHOPHYSIOLOGY:

- Unknown trigger → ANCA antibodies → vasculitis of small vessels (arterioles, capillaries, venules)
- Previously called as a microscopic form of polyarteritis nodosa

PRESENTATION:

- Renal features (most common): glomerulonephritis, renal failure
- Constitutional features: weight loss, fever, fatigue, malaise, myalgias
- Dermatological features: palpable purpura usually on dependent areas e.g. feet, legs, buttocks; other lesions are papules, vesicles, livedo reticularis, skin ulcers
- Neurological features: mononeuritis multiplex, seizures
- Others: chest pain, hypertension, heart failure, GI bleeding, arthralgias, orchitis

INVESTIGATIONS:

- CBC: raised WBCs, normocytic anemia
- ESR and CRP: raised
- Renal function tests: raised urea and creatinine
- Urine D/R: proteinuria, hematuria, leukocyturia
- ANCA: p-ANCA (80%), c-ANCA (40%)
- Chest x-ray or CT: bilateral irregular nodular and patchy opacities or infiltrates, alveolar hemorrhages
- Skin biopsy: necrotizing arteritis with sparing of muscular vessels
- Open lung biopsy
- Renal biopsy

MANAGEMENT:

- Steroids + RITUXIMAB or CYCLOPHOSPHAMIDE

⇨ ***Small vessel vasculitis without asthma and granulomatous inflammation = MPA***

⇨ ***MPA is differentiated from PAN by: small vessel involvement in MPA***

⇨ ***MPA is differentiated from GPA by: absence of granulomas and upper respiratory tract involvement.***

9.12.8. HENOCH-SCHÖNLEIN PURPURA (HSP)

"It is an IgA-mediated generalized vasculitis affecting small vessels."

QUICK FACTS: HENOCH-SCHÖNLEIN PURPURA	
Pathology:	**IgA complexes in small vessels → leucocytoclastic vasculitis and crescentic glomerulonephritis**
Presentation:	**Headache, anorexia, fever and rash (on lower extremities, hands, arm, trunk and buttocks), arthritis, hematuria, abdominal pain and vomiting, bloody stools, renal failure**
Diagnosis:	**Diagnosis of exclusion**
Treatment:	**Hydrate, analgesics, steroids** **Renal involvement: azathioprine, mycophenolate mofetil**

PATHOGENESIS:

- IgA complexes deposit in small vessels → leukocytoclastic vasculitis.
- Renal lesions show segmental glomerulonephritis with crescents and mesangial deposition of IgA

PRESENTATION:

- Headache; anorexia; fever; rash (erythematous macules or urticarial → blanching papules → palpable purpura typically on dependant areas like lower extremities, hands, arms, trunk and buttocks); arthritis (mostly knees and ankles); hematuria; abdominal pain and vomiting; bloody stools.
- Adults typically develop renal failure while children typically develop abdominal vasculitis.

INVESTIGATIONS:

- No specific diagnostic test is available. Exclude other causes of vasculitis.

TREATMENT:

- Hydrate adequately. Analgesics for joint pain.
- Steroids: PREDNISONE 1 mg/kg/day PO
- If renal involvement: AZATHIOPRINE or MYCOPHENOLATE MOFETIL

⇨ ***It is the most common systemic vasculitis in children.***

9.12.9. CRYOGLOBULINEMIA

"It is a condition caused by presence of cryoglobulins in blood - antibodies which precipitate in cold and dissolve on rewarming."

QUICK FACTS: CRYOGLOBULINEMIA	
Pathology:	**Cryoglobulins → hyperviscosity and autoimmune features**
Presentation:	**Type 1: asymptomatic, hyperviscosity features** **Type 2 and 3: arthralgia, myalgia, MPGN, cutaneous vasculitis, peripheral neuropathy**
Diagnosis:	**RA factor: raised** **C4: low** **Cutaneous or renal biopsy** **Workup of underlying cause**
Treatment:	**Type 1: plasmapharesis, treat underlying cause** **Type 2 and 3: prednisone +/- immunosuppressants** **HCV-related: prednisone → interferon alfa + ribavirin**

EPIDEMIOLOGY:

- Age: 45- 50 years
- Gender: female:male ratio = 3:1

TYPES (ACCORDING TO ANTIBODY TYPE):

- Type 1 (simple):
  - Is characterized by a monoclonal antibody devoid of RA factor activity.
  - Associated with lymphoma, Waldenstrom's macroglobulinemia and multiple myeloma.
  - Do not activate complement.
  - Presentation: asymptomatic (mostly), hyperviscosity syndrome
- Type 2:
  - Monoclonal rheumatoid factors (antibodies against Fc portion of IgG).
  - Associated with lymphoproliferative diseases, rheumatic diseases, chronic infections, CLD and hepatitis C.
- Type 3:
  - Polyclonal rheumatoid factors
  - Associated with rheumatic diseases (SLE, systemic sclerosis), chronic infections, CLD and hepatitis C.

TYPES (ACCORDING TO ETIOLOGY):

- Essential cryoglobulinemia: absence of underlying conditions.
- Secondary cryglobulinemia: due to some other underlying disorder e.g. SLE

PRESENTATION:

Type 1 typically presents as:

- Asymptomatic
- Hyperviscosity features: acrocyanosis, retinal hemorrhages, Raynaud's phenomenon, livedo reticularis, purpura, nail-fold capillary abnormalities, arterial thrombosis (e.g. digital or renal)

Type 2 and 3 typically present as:

- Arthralgias, fatigue, myalgias, renal immune-complex disease (MPGN), cutaneous vasculitis (lower extremity purpura), peripheral neuropathy and pulmonary infiltrates

INVESTIGATIONS:

- RA factor: raised in types 2 and 3
- Low C4
- Urine D/R: hematuria, proteinuria
- HCV testing
- Workup of underlying cause
- Biopsy: cutaneous or renal

MANAGEMENT:

- Type 1: plasmapharesis, chemotherapy of underlying disease
- Type 2 and 3:
  - No treatment needed for mild purpura.
  - Severe disease or essential variety: prednisone +/- cyclophosphamide or azathioprine or rituximab
  - Hepatitis C associated disease: prednisone followed by interferon alfa + ribavirin

9.12.10. BEHÇET SYNDROME

"It is an autoimmune multi-system vasculitic disease due to abnormal lymphocyte function and neutrohilic hyperfunction leading to both arterial and venous vassculitis."

QUICK FACTS: BEHÇET SYNDROME	
Pathology:	**Unknown antigen → abnormal T-lymphocyte function → neutrophil hyperfunction → vasculitis, endothelial cell dysfunction, hypercoagulability**
Presentation:	**Usually middle-eastern men** **Recurrent oral and genital ulcers**

	Uveitis, hypopyon **Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular rash)** **Arthralgias and arthritis** **Venous and arterial thromboses**
Diagnosis:	**Pathergy test: positive** **Biopsy**
Treatment:	**Colchicine, steroids, immunosuppressants**

EPIDEMIOLOGY:

- Age: usually 30 – 40 years
- Gender: male:female ratio = variable (more severe in males)
- Location: Asians, , Middle-easterners, Mediterraneans, Turkish
- Genetics: HLA-B51

PATHOPHYSIOLOGY:

- Unknown antigens → abnormal T-lymphocyte function → neutrophil hyperfunction → vasculitis, endothelial cell dysfunction and hypercoagulability

PRESENTATION:

- Oral features: recurrent aphthous ulcers (painful, non-scarring, appear in crops)
- Genital ulcers: painful scarring ulcers on vulva and vagina (in females), penis and scrotum (in males)
- Ocular features: uveitis, hypopyon
- Dermatological features: erythema nodosum, pseudofolliculitis, papulopustular rash, acneiform nodules
- Musculoskeletal features: arthralgia/ arthritis (mostly knees and ankles), rarely myositis
- Gastrointestinal features: ulcers (mostly in ileocecal region), mesenteric ischemia/ infarction, perforation
- Neurologic features: meningitis, meningoencephalitis, psychiatric symptoms (personality changes, hallucinations), neurological deficits, brain-stem lesions
- Vascular features: venous thromboses > arterial thromboses, migratory superficial thrombophlebitis, Budd-Chiari syndrome, SVC syndrome, cerebral venous thromnoses, arterial ischemia
- Pulmonary features: pulmonary vasculitis and arterial aneurysms → hemoptysis, dyspnea, cough, chest pain
- Cardiac features: culture-negative endocarditis, vegetations, embolization

INVESTIGATIONS:

- CBC: normocytic anemia
- Anti-cardiolipin antibodies (30%)
- CSF: may show pleocytosis
- Angiography: aneurysms, thrombosis
- CT or MRI brain: focal lesions, enlarged ventricles
- Biopsy of involved area

MANAGEMENT:

- For oral and genital ulcers: topical steroids or sucralfate
- Colchicine
- Steroids
- Immunosuppressants
- Anticoagulation where needed

⇨ ***Classical presentation of Behçet's syndrome: recurrent aphthous ulcers, genital ulcers, uveitis and retinal vasculitis leading to blindness.***

Table 9.35: INTERNATIONAL DIAGNOSTIC CRITERIA FOR BEHÇET DISEASE
• Recurrent oral ulcerations PLUS any two of the following: • Recurrent genital ulcerations • Eye lesions (anterior uveitis, posterior uveitis) • Cells in vitreous • Retinal vasculitis • Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules) • Positive pathergy test

9.12.11. PRIMARY ANGIITIS OF CNS

Aka cerebral angiitis

"It is a small and medium vessel vasculitis which is limited to brain and spinal cord."

PRESENTATION:
- Headaches, neurological deficits, stroke, seizures

DIAGNOSIS:
- Diagnosis of exclusion

MANAGEMENT:
- Steroids

9.13. AMYLIDOSIS

"It is a systemic disorder characterized by extracellular deposition of amyloid."

QUICK FACTS: AMYLOIDOSIS	
Pathology:	**Deposition of amyloid fibrils in different organs**
Presentation:	**Fatigue, weight loss, restrictive cardiomyopathy, conduction defects, neuropathies, proteinuria, malabsorption, macroglossia, organomegaly, raised waxy papules**
Diagnosis:	**Serum immunofixation and free light chains** **Biopsy of abdominal fat pad, rectum, involved organs: apple-green birefringence on congo-red stain**
Treatment:	**No specific treatment** **Treat underlying cause** **Melphalan, prednisone, autologous stem cell transplantation (AL type)**

TYPES:
- AL type (immunoglobulin light-chain deposition):
  - Examples: primary amyloidosis, multiple myeloma, light chain disease, MGUS, Waldenström's macroglobulinemia
- AA type (serum amyloid-A deposition):
  - RA, chronic infections or inflammations (e.g. osteomyelitis, TB), Familial Mediterranean fever, IBD, renal cell carcinoma
- Aβ2M type:
  - β2-microglobulin disease in hemodialysis patients
- others:
  - Transthyretin deposition in familial amyloid polyneuropathy, calcitonin deposition in medullary carcinoma of thyroid

EPIDEMIOLOGY:
- Age: elderly

- Gender: male:female ratio equal

PATHOPHYSIOLOGY:

- Conformational changes in precursor proteins → insoluble amyloid → polymerize to form amyloid fibrils → deposition in various organs

PRESENTATION:

- General: fatigue, weight loss
- Cardiac: restrictive cardiomyopathy, conduction defects
- Neurologic: distal neuropathies, autonomic neuropathies, carpal tunnel syndrome
- Renal: proteinuria, nephrotic syndrome, renal tubular acidosis
- Gastrointestinal: malabsorption, macroglossia, hepatomegaly, intra-hepatic cholestasis, splenomegaly
- Rheumatologic: symmetric arthritis
- Hematological: acquired factor X deficiency
- Dermatological: raised waxy papules, peri-orbital ecchymosis, pinch purpura

INVESTIGATIONS:

- Serum immunofixation and free light chains: for AL
- ECG: bradycardia, blocks, low-voltage QRS
- Urine D/R: proteinuria
- Albumin: low
- Biopsy of involved organs: preferably abdominal fat pad or rectum; bone marrow biopsy for AL type
- Histopathology: amorphous eosinophilic extracellular deposition; apple-green birefringence under polarized light microscopy after Congo-red staining

TREATMENT:

- Treat underlying cause
- No specific treatment of amyloidosis. Prognosis is poor.
- AL type: melphalan and prednisone prolongs survival, autologous stem cell transplantation

9.14. PERI-ARTICULAR DISORDERS

9.14.1. BURSITIS

"It is a condition of inflamed bursae."

Common types of bursitis include:

- Anterior Achilles tendon bursitis/ retrocalcaneal bursitis/ Albert's disease:
  - Pain, swelling and warmth around heel anterior to Achilles tendon; difficulty walking and wearing shoes.
  - Risk factors: Strain on Achilles tendon or gout leads to inflammation.
- Posterior Achilles tendon bursitis/ Achilles bursitis:
  - Pain, warmth and redness at back of heel behind Achilles tendon.
  - Risk factors: strain on heel, wearing high-heels, heel deformity.
- Trochanteric bursitis/ hip bursitis:
  - Painful swelling at greater trochanteric region of lateral hip.
  - Risk factors: trauma, osteoarthritis
- Olecaranon bursitis/ elbow bursitis/ students elbow:
  - Painful swelling over proximal end of ulna.
  - Risk factors: injury or repeated friction to elbow.
- Knee bursitis/ pes Anserine bursitis/ goosefoot bursitis:
  - Painful, tender inner knee, swelling at inner knee
  - Risk factors: lack of stretching before exercise, obesity, arthritis, etc.
- Pre-patellar bursitis/ knee-cap bursitis/ house-maid's knee:
  - Painful swelling in front of patella.
  - Risk factors: sitting on knees for long periods e.g. house-maid's, plumbers.

- Sub-acromial bursitis:
    - Pain in shoulder (front and sides).
    - Risk factors: RA, gout, infection

MANAGEMENT:

- Rest
- NSAIDs
- Intra-bursal steroids
- Physiotherapy
- Surgical treatment

9.14.2. ROTATOR CUFF TENDONITIS

- It is inflammation of tendons and muscles which form the rotator cuff.
- Rotator cuff is formed by tendons of supraspinatus, infraspinatus, teres minor and subscapularis.
- It presents as shoulder pain.
- Treatment is rest, NSAIDs, physiotherapy and local steroids.

9.14.3. BICIPITAL TENDONITIS

- It is inflammation of tendon of long head of biceps which is caused by wear and tear, trauma and impingment.
- It presents as shoulder pain (anterior area) which is increased by lifting, pushing or pulling and over-head activities.
- It is treated with NSAIDs, loal steroids, rest, physiotherapy and occupational therapy.

9.14.4. DEQUERVAIN'S TENDONITIS

- It is inflammation of tendons and sheaths of abductor pollicis longus and extensor pollicis brevis from repetitive movements of thumb and wrist.
- There is pain and swelling in the anatomical snuff box at wrist.
- Treatment is rest, fomentation, NSAIDs and physiotherapy.

9.14.5. ADHESIVE CAPSULITIS/ FROZEN SHOULDER

- There is restriction of motion of shoulder (elevation, external rotation and internal rotation) with pain at extremes of motion
- It is associated with diabetes.
- Treatment is intra-articular steroids, NSAIDs, physiotherapy

9.14.6. MEDIAL EPICONDYLITIS/ GOLFER'S ELBOW

- It is inflammation of medial epicondyle of humerus.
- It is usually seen in golfers.
- Pain occurs over medial epicondyle and is increased by flexing the wrist against resistance.
- Treatment is NSAIDs and local steroids.

9.14.7. LATERAL EPICONDYLITIS/ TENNIS ELBOW

- It is inflammation of common extensor tendon at lateral epicondyle usually caused by strain.
- Pain occurs in front of lateral epicondyle and is worse on extending the wrist against resistance.
- Treatment is rest, NSAIDs, local steroid injections, physiotherapy and surgical repair.

9.14.8. PLANTAR FASCIITIS

- It is inflammation of plantar fascia at its origin.
- It is the most common cause of heel pain.
- Examination shows tenderness at origin of plantar fascia and tenderness worsens with dorsiflexion of metatarsophalangeal joints.
- Treatment is with soft cushioning of feet, NSAIDs and physiotherapy.

9.15. BONE AND CARTILAGE DISORDERS

Metabolic bone diseases include:

- Osteoporosis
- Osteomalacia and rickets
- Osteitis fibrosa cystica
- Paget's disease of bone
- Renal osteodystrophy
- Osteopetrosis

Other disorders include:

- Osteomyelitis
- Spinal tuberculosis
- Osteonecrosis

9.15.1. OSTEOPOROSIS

"It is a condition of decreased which predisposes to increased risk of fracture."

QUICK FACTS: OSTEOPOROSIS	
Pathology:	**Decrease in bone mass → predisposes to fractures**
Presentation:	**Asymptomatic** **Backache** **Fragility fractures (vertebral, hip and others)**
Diagnosis:	**DEXA scan, quantitative CT scan**
Treatment:	**Bisphosphonates (first choice)** **Hormone therapy (post-menopausal women with vasomotor symptoms)** **SERMs, calcitonin, strontium ranelate, denosumab, teriparatide** **Adequate calcium, vitamin D intake**

- 10% decrease in bone mass increases the risk of vertebral fracture by 2 times and hip fracture by 2.5 times.
- 61% of osteoporotic fractures occur in women.
- Women and men over the age of 50 years have increased risk of fractures.
- Major osteoporotic fracture: hip, vertebra, forearm, proximal humerus.
- Hip and vertebral fractures have increased risk of death after fractures.

Table 9.36: RISK FACTORS FOR OSTEOPOROSIS	
Age ≥50 years	**Age <50 years**
Age ≥65 years Risk factors for osteoporosis (post-menopausal women and 50 – 64 year old males): History of fragility fracture after age 40 years Prolonged use of steroids (3 months cumulative therapy of ≥7.5 mg/day of prednisone-equivalent dose in previous year) Use of other high-risk medicines e.g. aromatase inhibitors, anti-androgens Family history of hip fracture Vertebral fracture or osteopenia on x-ray Current smoking Consumption of >2.5 units of caffeine daily (1 unit = 1 cup coffee or two cups of tea) High alcohol intake (>14 units/ week for women and >21 units/ week for men) Low body weight (<60 kg) or loss of weight (>10% at age 25 years) Rheumatoid arthritis Others disorders strongly associated with osteoporosis	History of fragility fracture Prolonged use of steroids Use of other high-risk medicines e.g. aromatase inhibitors, anti-androgens Hypogonadism or premature menopause (age <45 years) Others disorders strongly associated with osteoporosis
Others disorders strongly associated with osteoporosis include: Primary hyperparathyroidism Type I diabetes Osteogenesis imperfecta Untreated long-standing hyperthyroidism, hypogonadism or premature menopause Cushing's disease Chronic malnutrition or malabsorption Chronic liver disease Chronic inflammatory conditions e.g. IBD **Other risk factors:** Physical inactivity Chronic hyponatremia Genetic diseases e.g. aromatase deficiency, Marfans syndrome History of fracture Certain races e.g. Asians, Latinos Low calcium diet Hypovitaminosis D Excessive vitamin D or vitamin A intake Anorexia nervosa Medications e.g SSRIs, thiazolidinediones (pioglitazone, rosiglitazone), anti-convulsants (phenobarbital, phenytoin), anti-retroviral drugs, cyclosporine, heparin, lithium, proton pump inhibitors, tacrolimus, methotrexate	

EPIDEMIOLOGY:

- Age: usually after 50 years of age
- Gender: usually post-menopausal women

PRESENTATION:

- Asymptomatic
- Backache
- Fragility fractures
    - Vertebral fracture and collapse, loss of height (two-third of fractures are painless)
    - Hip fracture
    - Other fractures e.g. Colles fracture, shoulder fractures, pubic and sacral fractures

INVESTIGATIONS:

- Calcium, phosphate, PTH: normal
- Alkaline phosphatase: normal or slightly elevated especially if there is fracture
- Vitamin D: may be low
    - Check in following patients:
        - Planned for osteoporosis treatment
        - Those with history of recurrent fractures
        - Those with malabsorption
        - Those who suffer bone loss despite osteoporosis treatment

- Dual energy x-ray absorptiometry (DEXA): shows bone mineral density (BMD)
    - T-score represents patient's BMD as a standard deviation from young normal mean. It is used in post-menopausal women.
    - Z-score represents patient's BMD as a standard deviation from an age-matched, race-matched and gender-matched individual. It is used in pre-menopausal women, younger men and children.
- Quantitative CT scan
    - More accurate in tall and short patients but exposes to more radiation
- Workup for risk factors e.g. TSH, SPEP, cortisol, testosterone, LH, FSH, SHBG, prolactin, urinary calcium excretion, creatinine, etc.
- Other tests: CBC, ESR, CRP, albumin, lateral radiographs of spine,

Screening recommendations:

- Screen all women ≥65 years of age [USPSTF]
- Screen women <65 years of age if 10-year fracture risk is greater than or equal to that of a 65 year old lady [USPSTF]
- Although not recommended but can consider males with a minimal trauma fracture who are older than 50 years or those with secondary causes [USPSTF]
- Screen all men ≥70 years of age [National Osteoporosis Foundation]
- Fracture risk assessment: FRAX questionnaire or QFracture questionnaire
- Screening methods:
    - Central DEXA scan
    - Peripheral DEXA scan (not reliable)
    - Annual height (>2% loss indicates silent vertebral fracture)
    - X-rays

Table 9.37: BONE MINERAL DENSITY CRITERIA FOR AGE ≥50 YEARS	
T-SCORE (in terms of standard deviations)	**STATUS OF BONE MINERAL DENSITY**
≥-1.0 SD	Normal BMD
-1.0 to -2.5 SD	Osteopenia
<-2.5 SD	Osteoporosis
<-2.5 SD with a fracture	Severe osteoporosis
BONE MINERAL DENSITY CRITERIA FOR AGE <50 YEARS	
Z-SCORE	**STATUS OF BONE MINERAL DENSITY**
≤ -2.0	Below expected range for age
> -2.0	Above expected range for age

MANAGEMENT:

General measures:

- Adequate diet: diet rich in proteins, calories, calcium and vitamin D
- Promote physical activity especially resistance training
- Stop or reduce if patient on long-term steroids
- Prevent falls e.g. cane, walkers
- Avoid alcohol and smoking
- Decrease caffeine intake
- Sunlight exposure

Supportive measures:

- Calcium
    - Should be added in patients on low-calcium diets
    - Increase incidence of myocardial infarction and renal stone disease so supplementation should be judicious.
    - Ensure adequate vitamin D
    - Treatment options
        - CALCIUM CITRATE 0.4 – 0.7 g elemental calcium daily or
        - CALCIUM CARBONATE 1 – 1.5 g elemental calcium daily
- Vitamin D
    - Replace in those with risk factors for low vitamin D and those with serum 25-hydroxyvitamin D levels <20 ng/ml
    - Keep checking vitamin D every 3 – 4 months till levels >30 ng/ml

- Treatment options
  - Sunlight exposure
  - 400 – 1000 IU for healthy adults
  - 800 – 2000 IU daily especially if risk factors for hypovitaminosis

Pharmacological measures:

- Bisphosphonates
  - Inhibit osteoclast-induced bone resorption
  - Oral bisphosphonates must be taken with at least 8 oz of water. Patient should remain upright for at least 30 minutes and must not eat anything for at least 40 minutes.
  - Bisphosphonates:
    - ALENDRONATE 10 mg orally daily OR 70 mg once weekly for treatment. Half the dose for prevention.
    - RISEDRONATE 5 mg orally daily OR 35 mg once weekly OR 150 mg once monthly.
    - ETIDRONATE cyclical therapy of 200 mg orally daily for 14 days followed by calcium supplementation for 10 weeks.
    - IBANDRONATE 2.5 mg orally daily or 150 mg orally once monthly or 3 mg iv every 3 months
    - ZOLEDRONIC ACID 5 mg iv over at least 15 – 30 minutes once annually for treatment and every two years for prevention.
    - PAMIDRONATE 30 – 60 mg iv every 3 – 6 months
  - Side-effects: reflux esophagitis, acute phase response (flu-like reaction), osteonecrosis of jaw, atypical chalk-stick fractures of femur, increased risk of esophageal cancer
- Sex hormones
  - Hormone therapy is recommended for post-menopausal women with moderate to severe vasomotor symptoms.
  - These reduce vertebral, non-vertebral and hip fractures.
- Selective estrogen receptor modulators (SERMs)
  - Raloxifene reduces risk of vertebral fractures but does not appear to reduce non-vertebral fractures.
  - Dose: 60 mg daily
  - Side-effects: hot flashes, leg cramps, thromboembolic events, pulmonary embolism.
  - Contraindicated if history of thromboembolic events, pregnant or breast-feeding.
- Calcitonin
  - Increases bone mass. Decreases pain in fractures.
  - Dose: 200 IU intranasal puff once daily alternating nostrils
  - Side effects: rhinitis, epistaxis, nausea, flushing
- Denosumab
  - It is a monoclonal antibody which binds to osteoclast receptor activator of nuclear factor-kappa B ligand (RANKL).
  - It inhibits maturation of preosteoclasts into mature cells.
  - Dose: 60 mg subcutaneously every 6 months
  - Side-effects: hypocalcemia, eczema, dermatitis, muscular and joint pains, infections, risk of malignancies
  - Contraindications: pregnancy, hypocalcemia
- Teriparatide
  - Compared to other agents it is bone-forming agent.
  - It is an analog of PTH.
  - It should be given with sufficient vitamin D and calcium.
  - Dose: 20 µg subcutaneously daily for 2 years.
  - Side-effects: headache, nausea, dizziness, hypercalcemia, renal calculi
  - It should not be used in patients with Paget's disease of bone, hypercalcemia, history of osteosarcoma or chondrosarcoma.
- Strontium ranelate

WHOM TO TREAT:

- Women with history of fragility fracture → BMD measurement not necessary although may be done → treat with drugs
- Postmenopausal women and men with [NOF]
    - Personal history of hip or vertebral fracture
    - Osteoporosis on BMD
    - Osteopenia with 10-year probability of hip fracture ≥3% using FRAX
    - Osteopenia with 10-year probability of any major fracture ≥20% using FRAX
- Presence of risk factors:
    - 10-year probability low: reassure, life-style changes
    - 10-year probability intermediate: check BMD (femoral)
        - If BMD shows low risk for fracture: life-style changes
        - If BMD shows intermediate risk for fracture: treat those with strong risk factors e.g. history of hip fracture in parents, history of use of steroids or presence of secondary causes.
        - If BMD shows high risk for fracture: treat
    - 10-year probability high: treat

CHOOSING THERAPY IN PATIENTS AT RISK:

- Post-menopausal women:
    - Alendronate, risedronate, zoledronic acid, denosumab for vertebral and non-vertebral fractures
    - Raloxifene for vertebral fractures
    - Calcitonin or etidronate for vertrebral fractures if intolerant of first-line therapies
- Post-menopausal women with moderate to severe vasomotor symptoms:
    - Hormone therapy for vertebral, non-vertebral and hip fractures
- Men:
    - Alendronate, risedronate and zoledronic acid as first-line.
    - Strontium ranelate and teriparatide can also be used.
    - Testosterone should not be used.
- Patients on long-term glucocorticoids:
    - Alendronate, risedronate or zoledronic acid should be given along with steroids.
    - Teriparatide should be considered if high risk for fracture.
    - If intolerant of first-line therapies, consider calcitonin or etidronate.

MONITORING:

- For patients on treatment repeat BMD after 1 – 3 years
- If BMD stable or improving increase interval
- If low risk of fracture and no risk factors for bone loss, repeat at 5 – 10 years

Table 9.38: EFFECT OF FRACTURE REDUCTION USING DIFFERENT PHARMACOLOGICAL AGENTS

Drug	Vertebral fracture	Non-vertebral fracture	Hip fracture	Wrist fracture
Alendronate	YES (men as well)	YES (men as well)	YES (men as well)	YES
Ibandronate	YES	YES	UNCERTAIN	-
Risedronate	YES (men as well)	YES (men as well)	YES (men as well)	-
Etidronate	YES	-	-	-
Zoledronic acid	YES (men as well)	YES (men as well)	YES (men as well)	-
Denosumab	YES	YES	YES	-
Raloxifene	YES	UNCERTAIN	-	-
Strontium ranelate	YES (men as well)	YES (men as well)	YES (men as well)	-
Teriparatide	YES (men as well)	YES (men as well)	UNCERTAIN	-
PTH (1-84)	YES	UNCERTAIN	UNCERTAIN	-

⇨ ***Osteoporosis is the most common metabolic bone disease.***

9.15.2. OSTEOMALACIA AND RICKETS

"Osteomalacia is incomplete mineralization of normal osteoid tissue following closure of epiphyses."
"Rickets is incomplete mineralization of normal osteoid tissue before closure of epiphyses."

QUICK FACTS: OSTEOMALACIA AND RICKETS	
Pathology:	**Deficiency of vitamin D or resistance to its action →**
Presentation:	**Adults: asymptomatic, diffuse bone and joint pain, proximal myopathy, waddling gait, hypotonia**
Diagnosis:	**Calcium, phosphorus, alkaline phosphatase, 25-hydroxy vitamin D, 1,25-hydroxy vitamin D, PTH** **x-rays**
Treatment:	**Sunlight exposure, vitamin D supplementation** **Calcium supplementation**

- 5-dihydrotachysterol in skin → ultraviolet exposure → forms cholecalciferol (vitamin D3) → undergoes 25-hydroxylation in liver → forms 25-hydroxycholecalciferol (calcidiol) → undergoes 1-hydroxylation in kidney → forms 1,25-dihydroxycholecalciferol (calcitriol) → binds to vitamin D receptor (VDR) in nucleus → 1) increases absorption of calcium and phosphate from intestine 2) increases phosphate reabsorption from kidney 3) increased deposition in bone

Note: Vitamin D2 (ergocalciferol) is a synthetic analog which is eliminated more rapidly as compared to D3. Therefore it has to be given daily to increase 25-hydroxy vitamin D levels

CAUSES:

- Vitamin D deficiency (aka classical rickets/ nutritional rickets):
  - Cause: acquired vitamin D deficiency
- Vitamin D dependent rickets:
  - Type 1 or pseudo-vitamin D deficiency rickets (VDDR1):
    - Cause: autosomal recessive mutation in gene encoding 1 α-hydroxylase → decrease in calcitriol → decrease in vitamin D response
    - 25-hydroxy vitamin D increases on supplementation in type 1a but does not increase in type 1b.
  - Type 2 or hereditary vitamin D-resistant rickets (VDDR2 or HVDRR):
    - Cause: autosomal recessive VDR gene mutation → does not bind calcitriol → decrease in vitamin D response
    - They characteristically have alopecia.
- Vitamin D resistant rickets/ X-linked hypophosphatemia/ X-linked hypophosphatemic rickets
  - Cause: X-linked dominant mutations in certain genes (e.g. PHEX) → increased fibroblat growth factor 23 (FGF23) → kidneys fail to absorb phosphate → phosphaturia → osteomalacia
  - Can be X-linked recessive or autosomal dominant in few families
- Renal rickets:
  - Cause: decreased formation of calcitriol due to renal damage
- Hypophosphatasia:
  - Cause: autosomal recessive or rarely autosomal dominant mutation in ALPL gene → abnormal alkaline phosphatase production → poor mineralization
  - Characteristically causes loss of teeth and arthralgias. Bone deformities occur in children.
- Hypocalcemia
  - Cause: low calcium → ineffective mineralization
- Hypophosphatemia
  - Cause: low phosphate → ineffective mineralization

PRESENTATION:

- In neonates:
  - Generalized hypotonia

- Craniotabes
- In children:
  - Frontal bossing
  - Delayed closure of anterior fontanelle
  - Deformities of weight bearing bones e.g. bow-legs, knock-knees
  - Cupping of epiphyses
  - Rachitic rosary (swelling at costochondral junctions)
  - Vertebral softening (kyphoscoliosis)
- In adults:
  - Asymptomatic (radiological osteopenia)
  - Diffuse bone and joint pain (usually lower back, pelvis, hips, legs and ribs – can be detected by pressure on sternum or tibia
  - Muscle weakness (usually proximal and more pronounced at thighs)
  - Difficulty walking (waddling gait with slow pace)
  - Decreased muscle tone

INVESTIGATIONS:

- Calcium, phosphorus, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D, PTH, alkaline phosphatase
  - 25-hydroxy vitamin D: usually <37 nmol/L (<15 ng/mL) – most sensitive marker
    - Vitamin D deficiency: <20 ng/mL
    - Vitamin D insufficiency: 21 – 29 ng/mL
    - Screening recommended in osteoporosis, obesity, malabsorption syndromes, disorders of vitamin D and phosphate metabolism
  - 1,25-dihydroxy vitamin D may be raised because of PTH (does not reflect deficiency)
- Imaging:
  - Widened growth plates in long bones and costochondral junctions (before epiphyseal fusion)
  - Decreased cortical thickness and radiolucency (after epiphyseal fusion)
  - Looser's zones/ pseudofractures

Table 9.39: TYPES OF OSTEOMALACIA

	Ca	Phos	Alk Phos	PTH	25-OH D	1,25-OH D	Urine studies	Others
Vitamin D deficiency	**N/ ↓**	**N/ ↓**	↑	↑	↓	↓/↑	**u. PO4 ↑ u. Ca N/↑**	Aminoacids ↑
Hypocalcemic rickets	↓		↑	↑	**N**	↑	**u. PO4 N/↑ u. Ca ↓**	**-**
Vitamin D dependent rickets type 1	**N/↓**	↓	↑	↑	**N/↑ (1a) ↓↓ (1b)**	**↓↓ (1a) Variable (1b)**	**u. PO4 ↑ u. Ca ↓**	**-**
Vitamin D dependent rickets type 2	↓	↓	↑	↑	**N/↑**	↑↑	**u. PO4 ↑ u. Ca ↓**	**-**
Vitamin D resistant rickets type 1	**N/ ↓**	↓	↑	↑	**N**	↓	**u. PO4 ↑ u. Ca N/↓**	**FGF23 ↑**
Vitamin D resistant rickets type 2	**N/ ↓**	↓	↑	↑	**N**	↑	**u. PO4 ↑ u. Ca N/↓**	**FGF23 ↑**
Hypophosphatasia	↑	↑	↓↓	↑	↑	↑	**u. PO4 N/↓ u. Ca ↓**	**-**
Renal osteodystrophy	↓	↑	**N/↑**	↑	**N/↓**	↓↓	**u. PO4 N/↓ u. Ca N/↑**	**-**

TREATMENT:

Note: RDI of vitamin D is 600 IU/day (≤70 years) or 800 IU/day (>70 years)

- Sunlight exposure (most useful and effective method in young)
- Vitamin D replacement:
  - In case of deficiency:
    - Adults: 50,000 IU D2 or D3 once weekly for 8 weeks OR 6000 IU/day of D2 or D3 for 8 weeks. Once 25-hydroxy D levels >30 ng/mL maintenance dose is 600 – 1000 IU/day.

        - Patients with obesity, malabsorption syndrome or drugs which interfere with vitamin D metabolism: 6000 – 10,000 IU once daily. Once 25-hydroxy D levels >30 ng/mL maintenance dose is 3000 – 6000 IU/day.
    - For vitamin D resistance: high doses of vitamin D
- High calcium diet
- Calcium supplementation
- Genetic counseling

9.15.3. OSTEITIS FIBROSA CYSTICA

Aka von Recklinghausen's disease of bone

"It is replacement of bone tissue with fibrous tissue leading to formation of cyst-like brown tumors in and around bone."

- It is caused by hyperparathyroidism due to any cause.
- X-rays show radio-lucent areas in bone.
- Treatment is treatment of hyperparathyroidism.

9.15.4. PAGET'S DISEASE OF BONE

Aka Osteitis deformans

"It is a localized disorder of bone with high bone turnover and disorganized osteoid formation."

QUICK FACTS: PAGET'S DISEASE OF BONE	
Pathology:	**Unknown trigger → osteoclastic overactivity → compensatory osteoblastic activity → disorganized osteoid with increased vascularity**
Presentation:	**Asymptomatic** **Bone pain, deformity, chalk-stick fractures** **High output cardiac failure, vascular steal syndromes** **Nerve compressions**
Diagnosis:	**Marker of bone formation: alkaline phosphatase** **Marker of bone turnover: C-telopeptide, PINP, urinary hydroxyproline, urinary deoxypyridinoline** **X-ray** **Bone biopsy**
Treatment:	**Bisphosphonates or calcitonin**

TYPES:

- Monostotic: involves one bone
- Polyostotic: involves >1 bones

EPIDEMIOLOGY:

- Age: usually 60 years
- Gender: male-female ratio is 1.8:1

PATHOPHYSIOLOGY:

Unknown trigger →

1. Lytic phase: osteoclastic over-activity
2. Mixed phase: compensatory osteoblastic activity
3. Sclerotic phase: disorganized osteoid (woven bone) with increased vascularity → infiltration of bone marrow by fibrous tissue and blood vessels

Note: Disease does not spread from one site to other.

PRESENTATION:

- Asymptomatic (70 – 90%)

- Bone pain (most common symptom)
- Due to weak osteoid: bone-deformity (e.g. bowed tibias, kyphosis, frontal bossing, enlarged maxilla, increased hat-size), chalk-stick fractures
- Due to increased vascularity: excessive warmth, high-output cardiac failure, vascular steal syndromes
- Neurological problems (usually due to nerve compressions in bony canals): deafness, cranial neuropathies, visual changes, cauda equina syndrome, spinal stenosis, basilar invagination (cerebellar or brain-stem compression)
- Associations: gouty arthritis
- Complications: secondary osteoarthritis, sarcomatous degeneration

INVESTIGATIONS:

- Markers of bone formation:
    - Alkaline phosphatase – markedly raised especially bone specific isomer BSAP
    - Osteocalcin (not useful)
- Markers of bone turnover: raised
    - Serum and urinary C-telopeptide (α- α type 1 C-telopeptide)
    - Urinary N-telopeptide of type I collagen OR procollagen I N-terminal peptide (PINP)
    - Urinary hydroxyproline
    - Urinary deoxypyridinoline
- Calcium: normal or high (in immobilized patients)
- Phosphate: normal
- PTH: normal
- Vitamin D: deficiency may be present
- X-rays: focal osteolytic areas (aka osteoporosis circumscripta)
- Bone biopsy

MANAGEMENT:

- Treatment is needed if:
    - Metabolically active disease
    - Need for orthopedic surgery at involved sites
    - Hypercalcemia or hypercalciuria
- Treatment options: cyclical bisphosphonates or calcitonin
    - ALENDRONATE 40 mg once daily for 3 – 6 monthly cycles
    - TILUDRONATE 400 mg once daily for 3 monthly cycles
    - RISEDRONATE 30 mg once daily for 2 monthly cycles
    - PAMIDRONATE 30 – 60 mg intravenously every 6 months
    - ZOLEDRONIC ACID 2 – 5 mg intravenously every 6 – 12 months
    - CALCTONIN 200 IU/unit nasal puff once daily alternating nostrils
- Monitoring should be done by serial bone markers.
- Treat complications accordingly

⇨ ***Paget's disease is the second most common bone disorder in elderly patients***.

9.15.5. METABOLIC BONE DISEASES IN CHRONIC RENAL DISEASE

9.15.5.1. RENAL DYSTROPHY

- Renal osteodystrophy is a spectrum of bone abnormalities in patients with chronic renal insufficiency.
- It includes: secondary hyperparathyroidism, rickets, osteomalacia, osteoporosis and adynamic bone disease.
- All patients with GFR <60 ml/min should have their calcium, phosphorus and PTH measured.
- Bone biopsy is the gold standard of diagnosis.
- Treatment includes dietary phosphorus restriction, calcium and vitamin D supplementation and phosphate binders.

9.15.5.2. ADYNAMIC BONE DISEASE

- It is a disease of low bone turnover due to suppression of PTH in end-stage renal disease.
- In uremia bone tissue is resistant to PTH so a higher than normal level is needed for bone turnover.
- It is suspected in patients with PTH levels <100 pg/mL.
- It is characterized histopathologically by reduced osteoclasts and osteoblasts, reduced or normal osteoid, and low bone turnover.
- It is caused by overtreatment of secondary hyperparathyroidism e.g. aggressive use of calcium-containing phosphate binders, aluminum containing antacids, high-calcium dialysate, vitamin D analogs and use of peritoneal dialysis.

9.15.6. PYOGENIC OSTEOMYELITIS

"It is inflammation of bone and/or bone marrow caused by an infectious organism."

QUICK FACTS: PYOGENIC OSTEOMYELITIS	
Pathology:	**Infection in bone and bone marrow**
Presentation:	**Fever, chills, night sweats, pain and tenderness of bone, chronic discharging sinus**
Diagnosis:	**X-ray bone, MRI, ultrasound** **Bone technetium scan or gallium scan** **Indium or technetium labeled white cell scans** **Bone biopsy**
Treatment:	**Parenteral antibiotics for 2 weeks followed by oral antibiotics for 4 weeks** **Surgery if unresponsive or vertebral osteomyelitis**

It is acquired by three routes:

1. Hematogenous dissemination
2. Invasion from nearby focus
3. Vascular insufficiency

RISK FACTORS FOR OSTEOMYELITIS:

- Sickle cell disease
- Intravenous drug abuser
- Diabetes mellitus
- Indwelling urinary catheters
- Elderly
- Infected prosthetic joints, neurosurgery
- Infective foci near joints e.g. decubitus ulcers, septic arthritis

CAUSES OF OSTEOMYELITIS:

- Staphylococcus aureus
- Pseudomonas
- Mycobacterium tuberculosis
- Gram negative infections e.g. Pseudomonas, Serratia.
- Hemophilus influenza

SITES FOR OSTEOMYELITIS:

- Hematogenous osteomyelitis: spine (most common and lumbar spine most common site), metaphyses of long bones, pelvis, clavicle.
- Contiguous-focus osteomyelitis: bones of feet, ankle
- Post-traumatic osteomyelitis: tibia

Vertebral osteomyelitis typically involves two adjacent vertebrae along with intervening vertebral disc.

CLINICAL FEATURES:

- Fever (usually high grade); chills; pain and tenderness of involved bone, malaise, night sweats.
- Chronic discharging sinus
- Features suggestive of osteomyelitis in a chronic ulcer: ulcer area >2 cm^2 AND positive probe test

INVESTIGATIONS:
- CBC: anemia of chronic disease, leukocytosis, raised ESR and CRP
- Blood cultures may be positive in cases of hematogenous spread
- Bone biopsy gives definitive diagnosis
- X-rays: periosteal thickening, cortical thickening, sclerosis, dead osteolytic bone (sequestrum) surrounded by new bone formation (involucrum).
- Bone technetium scan or gallium scan
- Indium or technetium labelled white cell scans
- MRI
- Ultrasound

COMPLICATIONS:
- Chronic or recurrent osteomyelitis
- Extension to adjacent bone or joint
- Amyloidosis.
- Nephrotic syndrome
- Marjolin ulcer (squamous cell carcinoma in the tract of draining sinus)
- Local abscesses in case of spinal osteomyelitis

TREATMENT:
- Parenteral antibiotics for 2 weeks followed by oral antibiotics for 4 weeks
- Usual antibiotics include clindamycin, rifampin, trimethoprim-sulfamethoxazole and fluoroquinolones
- Surgery if no response to antibiotics or in case of vertebral osteomyelitis with neurological compromise

⇨ ***Most common cause of osteomyelitis is Staphylococcus aureus.***
⇨ ***Most common cause of osteomyelitis in sickle cell anemia patients is Salmonella.***
⇨ ***Most common cause of osteomyelitis in iv drug abusers is Staphylococcus aureus.***

9.15.7. OSTEOPETROSIS

Aka marble bone disease

"It is an inherited disorder in which bones become hard and dense due to failure of osteoclasts to absorb bone."

PRESENTATION:
- Asymptomatic (may be incidentally disovered as bone sclerosis), bone pains, cranial neuropathies (e.g. facial palsy), fractures

INVESTIGATIONS:
- Calcium may be low; PTH, acid phosphatase, BSAP and CK-BB are increased

TREATMENT:
- Symptomatic treatment

9.15.8. SPINAL TUBERCULOSIS

Aka Pott disease or tuberculous spondylitis

"It is tuberculous infection of spine which leads to vertebral destruction."

QUICK FACTS: SPINAL TUBERCULOSIS	
Pathology:	**Tuberculous infection of vertebrae → arthritis and osteomyelitis**
Presentation:	**Back pain, radicular pain, fever, weight loss, gibbus, lower extremity weakness**
Diagnosis:	**X-ray, CT scan, MRI** **Abscess cultures, biopsy of lesions**
Treatment:	**ATT with steroids** **Surgical treatment**

AT RISK:

- Individuals from TB prevalent areas, immunocompromised (e.g. HIV infection, patients on anti-TNF drugs)

SITES:

- Mostly involves thoracic and lumbar vertebrae.

PATHOGENESIS:

- Hematogenous spread of Myocobacterium tuberculosis → infects anterior part of vertebral body and intervertebral disc → arthritis and osteomyelitis → may lead to collapse of vertebrae → deformity.
- Vertebral destruction may lead to → spinal cord compression or cauda equina syndrome → paraplegia.
- Inflammation may lead to → surrounding cold abscesses (paraspinal and psoas abscesses).

PRESENTATION:

- Back-pain; radicular pain; lower extremity weakness; fever; weight loss; gibbus deformity.

INVESTIGATIONS:

- Positive PPD or interferon-gamma release assay.
- Radiographs → lytic or sclerotic lesions, bony destruction
- CT scans → demonstrate abscesses
- MRI → detects neurological compressions
- Abscess cultures → isolate M. TB
- Biopsy of lesions → chronic inflammation with caseating granulomas

Treatment:

- Anti-tuberculous therapy for 6 – 9 months (some recommend 9 – 12 months).
- Intensive phase: Isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months.
- Continuation phase: Isoniazid and rifampicin for remaining months.
- Surgical treatment if deformity or neurological complications.

⇨ ***Back pain is the most common symptom of Pott's disease.***

9.15.9. OSTEONECROSIS

Aka Avascular necrosis (AVN)

"It is death of bone components due to interruption of blood supply."

QUICK FACTS: OSTEONECROSIS	
Pathology:	**Interruption of terminal blood supply → necrosis of bone marrow and bone**
Presentation:	**Mostly occurs in proximal end of femur** **Asymptomatic** **Pain in joint on weight bearing**
Diagnosis:	**X-ray, MRI, CT scan, radionuclide bone scan, biopsy**
Treatment:	**Analgesics, surgery**

RISK FACTORS:

- Drugs (corticosteroids, bisphosphonates, NSAIDs etc.), alcoholism, trauma, sickle cell disease, gout, pancreatitis, SLE, renal transplantation, Gaucher's disease, Caisson disease.

PATHOGENESIS:

- Bones which have single terminal blood supply e.g. head of femur → interruption of blood supply → necrosis of bone marrow, medullary and cortical bone.

SITES:

- Proximal end of femur (most common), distal end of femur, ankle, shoulder, elbow, carpals, talus, meta-tarsals, mandible, etc.

PRESENTATION:

- Symptoms:Asymptomatic; pain in joint (progressively worsens, initially on weight bearing and later on rest); loss of joint function e.g. limping.
- Signs: Tenderness of joint; restricted active and passive movements; neurological signs (if nerve compression).

INVESTIGATIONS:

- Plain radiographs; MRI (image of choice); CT scan; radionuclide bone scan; biopsy and histology (diagnostic).

TREATMENT:

- Limited weight bearing, immobilization.
- Analgesics.
- Surgical treatment: core decompression, bone grafting, total arthroplasty

⇨ ***Patients taking bisphosphonates in malignancy or anti-cancer drug denosumab characteristically develop AVN of jaw.***

⇨ ***Most common site of AVN is proximal head of femur.***

9.16. RHABDOMYOLYSIS

"It is the rapid breakdown of skeletal muscles resulting in leakage of myoglobin in blood."

QUICK FACTS: RHABDOMYOLYSIS	
Pathology:	**Muscle injury → increased intracellular calcium → activates proteases and caspases → cell death → release of myoglobin → causes tubular obstruction, ATN and vasoconstriction**
Presentation:	**Muscle pain, swelling, dark-colored urine, rapid rise in creatinine, oliguria, nausea, fever, vomiting**
Diagnosis:	**Urine dipstick blood >> RBCs on microscopy** **Increased CK, CPK, troponins, LDH, SGOT**

Treatment:	**Vigorous hydration to maintain urine output of 100 – 200 ml per hour** **Alkalinization therapy** **Diuretics if decreased output or overload** **Hemodialysis**

PATHOPHYSIOLOGY:

- Injury to muscle cells results in increased intracellular calcium → activates proteases and caspases → increased cell injury with leakage of myoglobin, uric acid and other enzymes → myoglobin binds to haptoglobin in plasma → excess myoglobin and/or uric acid is filtered in kidney and may get precipitated resulting in tubular obstruction, acute tubular necrosis and renal vasoconstriction.

CAUSES:

- Prolonged recumbency due to any cause including alcoholism, stroke, myocardial infarction, prolonged surgical procedures or unconsciousness; certain drugs (e.g. statins, fibrates, anti-Parkinsonism drugs, colchicine, anti-histamines, neuroleptics, anesthetic agents, quinine, protease inhibitors); heatstroke; muscular trauma or crush injury; child abuse; illicit drug use (e.g. cocaine); metabolic derangements (hypokalemia, hypophosphatemia or hypomagnesemia); inflammatory myopathies (dermatomyositis, myosistis, polymyositis), severe hypothyroidism, genetic predispositions (familial paroxysmal rhabdomyolysis, McArdle disease, phosphofructokinase deficiency, carnitine deficiency), snake-bites, viral or bacterial infections (influenza, coxsackievirus, Legionella, Plasmodium falciparum, etc.), severe burns, seizures, strenuous exercise, drowning, hypothermia, limb ischemia.

SYMPTOMS/ SIGNS:

- Muscle pains/ tenderness, soft tissue swelling, weakness and stiffness; dark-colored urine; oliguria, nausea, fever, vomiting. Most common muscles involved are calves and lower back.

INVESTIGATIONS:

- Urine analysis shows blood positive dipstick which is disproportionately more than RBCs in urine; elevated myoglobin in blood and urine; elevated CPK, aldolase, SGOT, SGPT, troponins and LDH. Aside from these CBC, electrolytes, urea, creatinine, PT and APTT are also needed. Peak CK level >15,000 units/l are highly predictive of renal failure.

COMPLICATIONS:

- Electrolyte derangements (hyperkalemia, hyperphosphatemia, early hypocalcemia, late hypercalcemia); hypoalbuminemia; hyperuricemia; compartment syndrome; acute renal injury; DIC.

TREATMENT:

- Assess circulation, airway and breathing.
- Identify and correct the triggering factor.
- Hydrate aggressively to prevent renal failure. Infuse isotonic fluids at a rate of ≥400 ml/hour.
- Do hourly urine output charting. Maintain a urine output of about 200 ml/hour.
- Correct electrolyte and acid-base abnormalities.
- Monitor for hyperkalemia.
- Supplement glucose or fructose in diet.
- Hemodialysis if develops renal failure.
- Fasciotomy if compartment syndrome develops.

⇨ ***Triad of rhabdomyolysis: Myalgias + Generalized weakness + Darkened urine***

⇨ ***CK rises within 12 hours, peaks in 24 – 36 hours and declines in 3 -5 days after resolution of muscle injury.***

10. ENDOCRINOLOGY AND METABOLISM

10.1. DISEASES OF PITUITARY GLAND

Anterior pituitary gland produces following hormones:

- Growth hormone (GH)
- Adreno-corticotropin hormone (ACTH) or corticotropin
- Thyroid stimulating hormone (TSH) or thyrotropin
- Gonadotropins
    - Luteinizing hormone (LH)
    - Follicle-stimulating hormone (FSH)
- Prolactin

Posterior pituitary produces following hormones (synthesized in hypothalamus):

- Oxytocin
- Anti-diuretic hormone (ADH)

These hormones are secreted in a pulsatile mechanism under influence of hormones from the hypothalamus. Hypothalamic hormones include:

- Growth hormone-releasing hormone (GHRH) – stimulates GH secretion
- Growth hormone-inhibiting hormone (GHIH) or somatostatin – inhibits GH secretion
- Thyrotropin-releasing hormone (TRH) – stimulates TSH secretion
- Corticotropin-releasing hormone (CRH) – stimulates ACTH
- Gonadotropin hormone releasing hormone (GnRH) – stimulates LH and FSH secretion
- Prolactin inhibitory factor or dopamine (PIF) – inhibits prolactin secretion

10.1.1. GROWTH HORMONE DEFICIENCY

It is associated with following features:

- Adults: increased cardiovascular diseases, obesity, muscle weakness, hypercholesterolemia
- Children: decreased height and growth

10.1.2. GROWTH HORMONE EXCESS

It can present as:

- Acromegaly
- Gigantism

10.1.2.1. ACROMEGALY

"It is excessive growth of acral and soft tissue parts due to excessive growth hormone secretion after closure of epiphyses."

QUICK FACTS: ACROMEGALY	
Pathology:	**Excessive growth hormone → increased IGF-1 from liver → growth of different parts**
Presentation:	**Growth of acral parts (hands, feet, jaw, tongue)** **Skin tags and hyperhidrosis** **Nerve entrapments** **Hypertension, insulin resistance, dilated ardiomyopathy, obstructive sleep apnea, degenerative arthritis, effects of pituitary tumor**
Diagnosis:	**Serum IGF-1, glucose challenge test, MRI brain**
Treatment:	**1st line: trans-sphenoidal surgery** **2nd line: somatostatin analogues, dopamine analogues, GH receptor antagonists**

PATHOPHYSIOLOGY:

- Excess production of growth hormone → release of insulin-like growth factor 1 (IGF 1) from liver and other tissues → growth of different tissues

CAUSES:

- Pituitary adenoma
- Ectopic secretion of GH or GHRH by a lymphoma, hypothalamic tumor, bronchial carcinoid or pancreatic tumor

PRESENTATION:

- Tissue enlargement: wide fingers (ring size increases), broad hands and feet, coarse face, hat size increases, prognathism, dental mal-occlusion, macroglossia, deep coarse voice (due to hypertrophy of pharyngeal and laryngeal tissue), obstructive sleep apnea, goiter
- Skin features: doughy moist skin, skin tags, acanthosis nigricans
- Hypertension
- Insulin resistance, diabetes
- Dilated cardiomyopathy
- Arthralgias and degenerative arthritis
- Changes due to pituitary tumor: hypogonadism, hyperprolactinemia, headahces, bitemporal hemianopia, secondary hypothyroidism
- Associations: MEN syndromes, McCune Albright syndrome, Carney complex

INVESTIGATIONS:

- Serum IGF 1 (screening test)
- Blood glucose challenge test:
    - Measurement of growth hormone one hour after oral administration of 100 g glucose: GH >10 ng/ml
- Prolactin: 20% of pituitary adenomas co-secrete prolactin
- MRI brain: for pituitary adenomas
- X-ray:
    - Skull: enlarged sella turcica
    - Hands and feet: tufting of terminal phalanges

MANAGEMENT:

- Trans-sphenoidal surgery (first-line treatment)
- If surgery fails:
    - Somatostatin analogs: OCTREOTIDE, LANREOTIDE
    - Dopamine analogs: CABERGOLINE, BROMOCRIPTINE
    - GH receptor antagonists: PEGVISOMANT
    - Selective estrogen receptor modulators: TAMOXIFEN
    - Stereotactic surgery
    - Radiation therapy

10.1.2.2. GIGANTISM

"Gigantism is abnormally high height due to excessive action of insulin-like growth factor while the epiphyses are open."

QUICK FACTS: GIGANTISM	
Pathology:	**Excessive growth hormone → increased IGF-1 from liver → growth of different parts**
Presentation:	**Tall height** **Rest of features as acromegaly**
Diagnosis:	**As acromegaly**

Treatment:	As acromegaly

Its presentation includes:

- Skeletal features: tall height, macrocephaly, enlarged hands and feet, frontal bossing, prognathism,
- Hyperhidrosis
- Carpal tunnel syndrome
- Due to growth of pituitary adenoma: headaches, hypopituitarism, visual changes (bitemporal hemianopia), endocrinopathies
- Dilated cardiomyopathy and heart failure

Investigations and management are the same as acromegaly.

10.1.3. HYPERPROLACTINEMIA

"It is a condition of excessive secretion of prolactin."

QUICK FACTS: HYPERPROLACTINEMIA	
Pathology:	**Excessive prolactin → hypogonadotrophic hypogonadism + breast epithelial growth + mass effects**
Presentation:	**Females: oligomenorrhea, infertility** **Males: decreased libido, erectile dysfunction** **Effects of pituitary tumor**
Diagnosis:	**Fasting prolactin levels (exclude other causes of raised prolactin)**
Treatment:	**Asymptomatic: monitor** **Symptomatic: control any causes, treat hypothyroidism, dopamine agonists, surgery in non-responsive**

- Prolactin is secreted from anterior pituitary gland.
- Its secretion is inhibited by dopamine (prolactin inhibitory factor) secretion from hypothalamus.
- Its secretion is stimulated by hypothalamic peptides, TRH, VIP, epidermal growth factor and dopamine antagonists.

It causes:

- Breast epithelial cell proliferation
- Suppresses secretion of GnRH → suppresses LH and FSH → suppresses estrogen and testosterone

Table 10.1: CAUSES OF RAISED PROLACTIN

PHYSIOLOGIC	PHARMACOLOGIC	ENDOCRINE	NON-ENODCRINE
Exercise Familial Pregnancy Post-partum period Non-fasting state	**Dopamine antagonists:** Phenothiazines Metoclopramide Sulpirides **Dopamine depleting agents:** Methyldopa Reserpine **Others:** Isoniazid Tricyclic anti-depressants Mono-amine oxidase Danazol Estrogens Anti-androgens Verapamil Cimetidine	**Prolactin secreting adenomas:** Micro-adenomas Macro-adenomas **Others:** Hypothyroidism Acromegaly Hypothalamic disease	Post-seizure state Chronic chest wall stimulation (chest wall surgeries, herpes zoster, mammoplasty) Chest wall trauma Cirrhosis Renal failure

PATHOPHYSIOLOGY:

- Hyperprolactinemia → Hypogonadotropic hypogonadism + breast epithelial growth + mass effects

PRESENTATION:

- Hypogonadotropic hypogonadism:
  - Females: oligomenorrhea, amenorrhea, infertility, decreased vaginal lubrication, irritability, depression, galactorrhea
  - Males: decreased libido, erectile dysfunction, gynecomastia

- Mass effects:
    - Visual field defects e.g. bitemporal superior quadrantanopia or bitemporal hemianopia
    - Headache
- Others:
    - Effects due to co-secretion of growth hormone
    - Peri-partum cardiomyopathy

INVESTIGATIONS:

- Fasting prolactin levels
- Workup for causes of hyper-prolactinemia
- Workup for hypopituitarism
- Visual field examination
- Imaging: MRI, helical CT
- Workup for osteoporosis

MANAGEMENT:

- Hyper-prolactinemia without symptoms: monitor
- Hyper-prolactinemia with symptoms: treatment
    - Stop offending drugs if possible
    - Treat underlying disorders e.g. hypothyroidism
    - Dopamine agonists: BROMOCRIPTINE, CABERGOLINE, QUINAGOLIDE for 12 – 24 months
    - Surgery usually trans-sphenoidal if non-responsive or resistant
    - Stereotactic radiosurgery
    - Chemotherapy

⇨ ***Most common finding in hyperprolactinemia is galactorrhea.***
⇨ ***Most common finding in case of prolactinoma is visual field defects.***

10.1.4. CUSHING'S DISEASE

- It is a syndrome of hyper-cortisolism caused by excessive secretion of ACTH from pituitary gland.
- Refer to 10.5.1. Cushing's syndrome
- Cushing's disease usually presents with classical features of hyper-cortisolism. Visual field disturbances, hypopituitarism or features of raised ICP (e.g. headache) may be seen.

10.1.5. NELSON'S DISEASE

- It is the increased pigmentation seen after bilateral adrenalectomy in cases of pituitary tumors due to excessive secretion of ACTH. Adrenalectomy deprives the tumor of negative feedback inhibition of cortisol, resulting in rapidly enlarging mass. It is prevented by pituitary radiotherapy after adrenalectomy. It is treated by surgical removal or radiotherapy.

10.1.6. DIABETES INSIPIDUS (DI)

"It is a condition of polyuria and polydipsia with passage of dilute urine caused by deficiency or resistance to action of antidiuretic hormone."

QUICK FACTS: DIABETES INSIPIDUS	
Pathology:	**Deficiency or resistance to ADH → polyuria**
Presentation:	**Polyuria, polydipsia, nocturia**
Diagnosis:	**Hypernatremia, dilute urine, decreased ADH** **Water deprivation test**
Treatment:	**Replace losses, desmopressin acetate**

TYPES:

- Central DI: there is decreased secretion of ADH.
- Nephrogenic DI: there is resistance to action of ADH.
- Gestational DI: there is excessive vasopressinase activity leading to decrease in DI.
- Dipsogenic DI (primary polydispisa): there is suppression of ADH due to increased thirst and fluid intake.

CAUSES OF CENTRAL DI:
- Primary (no identifiable lesion of pituitary or hypothalamus): e.g. Wolfram or DIDMOAD syndrome
- Secondary (damage to hypothalamus or pituitary): tumor, hypophysitis, infarction, hemorrhage, anoxic encephalopathy

PRESENTATION:
- Polyuria (usually >3 l of urine per day), polydipsia, nocturia
- Hypernatremia

INVESTIGATIONS:
- 24-hour urine volume
- Serum electrolytes: usually hypernatremia
- Urinalysis: decreased specific gravity
- Urine osmolality: decreased
- Plasma osmolality: increased
- Plasma ADH: decreased
- Water deprivation test

MANAGEMENT:
- Drink enough fluids to replace urinary losses
- Stop aggravating factors e.g. steroids
- If oral intake poor or hypernatremia: dextrose water
    - Decrease serum sodium by 0.5 mmol/l every hour
- Desmopressin acetate
    - Intranasal 100µg/mL: 0.05 – 0.1 ml every 12 – 24 hours
    - Oral: 0.05 mg twice daily and increased to 0.4 mg every 8 hours
    - It can also be given sublingually, intravenously, intramuscularly or subcutaneously.

10.1.7. PITUITARY TUMORS

"These are adenomas which arise from cells of anterior pituitary."

QUICK FACTS: PITUITARY TUMORS	
Pathology:	**Pituitary tumor growth → compression of surroundings + over-production of hormones**
Presentation:	**Compression: headache, field defects (bitemporal hemianopia), optic atrophy, Excess hormone secretion: hyperprolactinemia, acromegaly, Cushing Hormone deficiencies**
Diagnosis:	**MRI brain Hormone evaluation**
Treatment:	**Surgical resection for compression and hyper-secretion (except prolactinomas which are treated medically first)**

PATHOPHYSIOLOGY:
Pituitary adenomas cause disease by two mechanisms:
- Over-production of pituitary hormones
- Compression of local tissues

TYPES:
- Microadenomas (<10 mm)
- Macroadenomas (≥10 mm)

PRESENTATION:

- Over-production of pituitary hormones
  - Prolactin-secreting tumors: see hyper-prolactinemia
  - Growth hormone secreting tumors: see acromegaly/ gigantism
  - ACTH secreting tumors: Cushing disease
- Compression of local tissues:
  - Anatomical problems:
    - Headache
    - Visual loss due to compression of optic chiasm from below: pituitary adenomas cause bitemporal hemianopia or bitemporal superior quadrantanopia
      - May particularly cause loss of red color vision
    - Optic atrophy
    - Compression of cavernous sinuses: diplopia, ptosis, ophthalmoplegia, decreased facial sensation, post-ganglionic Horner syndrome
    - Extension into sphenoid sinuses: CSF rhinorrhea
  - Hormonal deficiencies e.g. deficiencies of GH, GnRH, TRH, panhypopituitarism
  - Pituitary apoplexy: it is an acute hemorrhage (hemorrhage into an adenoma) or infarction (ischemia due to Sheehan's syndrome) of pituitary gland.
    - Endocrine emergency
    - Presents with severe headache, nausea, vomiting, diplopia, bilateral visual changes, ptosis, hypotension, hypoglycemia
- Features of associated genetic familial syndromes: MEN 1, Carney syndrome, AIP syndrome

INVESTIGATIONS:

- T1-weighted MRI brain with pituitary cuts (plain and gadolinium contrast)
- Visual field assessment
- Hormone evaluation:
  - Prolactin
  - IGF-1, oral glucose tolerance test, TRH stimulation test
  - ACTH, 8:00 AM cortisol, 24-hour urinary free cortisol, dexamethasone suppression test, metyrapone test, petrosal sinus levels of CRH
  - TSH, LH, FSH, testosterone

MANAGEMENT:

- Initial choice of treatment for prolactinomas is medical treatment. Medical treatment can also be done in case of GH- or TSH-secreting tumors.
- Surgical resection is indicated for tumors causing local compression and hyper-secretion (except prolactinomas).
- For tumors invading outside sella turcica: debulking surgery, radiation.

⇨ ***Prolactinomas are the most common type of pituitary adenomas.***

10.1.8. HYPOPITUITARISM

"It is a syndrome of failure of production of one or more pituitary hormones."

QUICK FACTS: HYPOPITUITARISM	
Pathology:	**Deficiency of one or more pituitary hormones**
Presentation:	**Features of hormone deficiencies**
Diagnosis:	**Fasting sugars, serum sodium** **LH, FSH, estradiol, testosterone, thyroid profile, cortisol, ACTH, IGF-1, growth hormone stimulation test** **MRI brain**
Treatment:	**Hormone replacement** **Surgical resection of tumors**

- Panhypopituitarism = failure of production of all pituitary hormones

PRESENTATION:

- GH deficiency:
  - Congenital: hypoglycemia, jaundice, small penis, short stature
  - Acquired: Central obesity, reduced physical and mental energy, impaired concentration, impaired memory, depression, decreased muscle and bone mass, increased LDL cholesterol
- Gonadotropin deficiency:
  - Congenital: lack of pubertal development
  - Acquired: diminished libido, weight gain, impotence, infertility
- TSH deficiency:
  - Features of hypothyroidism
- ACTH deficiency:
  - Features of hypoadrenalism except dark skin
- Prolactin deficiency:
  - Failure of lactation in puerperium
- ADH deficiency:
  - Diabetes insipidus
- Panhypopituitarism:
  - Combined features of above
  - Dry pale wrinkled skin, apathetic countenance
- Features of mass lesions: e.g. headache, visual field defects (typically bitemporal hemianopia, bitemporal superior quadrantanopia and sometimes homonymous hemianopia)

Table 10.2: CAUSES OF HYPOPITUITARISM

HYPOPITUITARISM WITH MASS LESIONS	HYPOPITUITARISM WITHOUT MASS LESIONS	FUNCTIONAL HYPOPITUITARISM
Pituitary: Pituitary adenomas Craniopharyngiomas Other brain tumors or metastases or hematological malignancies Rathke cleft cysts Granulomas e.g. granulomatosis with polyangiitis, tuberculosis, cholesterol granulomas African trypanosomiasis Aneurysms Lymphocytic hypophysitis Immune checkpoint inhibitor hypophysitis e.g. anti-CTLA-4 agents, anti-PD-1 agents	**Congenital:** Congenital hypopituitarism Congenital adrenal hypoplasia Prader-Willi syndrome Kallmann syndrome Congenital GH deficiency **Acquired:** Cranial radiations Pituitary surgery Encephalitis Cerebral malaria Hemochromatosis Autoimmunity Bexarotene Sheehan syndrome Histiocytosis X	**GH deficiency:** Malnutrition, chronic kidney disease, opioids usage, ageing **LH, FSH deficiency:** Serious illness, malnutrition, alcoholism, anorexia nervosa, opioid therapy, Cushing syndrome, hyperprolactinemia **ACTH deficiency:** High-dose opioids, excess steroids **TSH deficiency:** Mitotane, bexarotene

INVESTIGATIONS:

- Fasting sugar: low
- Sodium: low
- Hypogonadotropic hypogonadism:
  - Males: low fasting serum total or free testosterone, low or normal LH
  - Females: low estradiol, low or normal FSH
- Hypothyroidism: low FT3 and FT4, low or normal TSH
- ACTH deficiency:
  - 8 – 9 AM cortisol: <3 µg/dL indicates adrenal insufficiency, 3 – 15 µg/dL is further evaluated with a cosyntropin test, >15 µg/dL usually excludes adrenal insufficiency
  - Low or normal ACTH
- GH deficiency:
  - Low IGF-1 levels (usually <84 µg/dL)
  - Provocative GH-stimulation test
- Others: MRI brain

MANAGEMENT:

- Life-time hormone replacement
- Trans-sphenoidal surgery for tumors
- Monitor for hypothyroidism when replacing GH
- Replace glucocorticoids:
    - Oral HYDROCORTISONE 10 – 20 mg in morning and 5 – 15 mg in afternoon
    - During severe illness: HYDROCORTISONE 50 mg IV 6-hourly
- Replace thyroid hormone:
    - LEVOHYROXINE 25 – 300 µg daily
    - Always replace glucocorticoids before replacing thyroid hormones
- Sex hormone replacement
    - Males:
        - Testosterone replacement if levels <150 ng/mL
        - Human chorionic gonadotropin in men with oligospermia
        - CLOMIPHENE
    - Females:
        - DHEA if levels <400 ng/mL
        - Fertility induction: CLOMIPHENE, FSH, hCG
- Replace GH:
    - Subcutaneous recombinant human growth hormone injections 0.2 mg thrice weekly in symptomatic adults

10.2. DISEASES OF THYROID GLAND

- Thyroid hormone is synthesized in thyroid gland. The gland consists of follicular cells and parafollicular cells.
- Iodine is incorporated into tyrosine inside follicular cells to form tri-iodothyronine (T3) and thyroxine (T4).
- Upon need, thyroid gland secretes T4 (mostly) and T3 (small amount). Para-follicular cells produce calcitonin.
- T4 is converted in peripheral blood to active form T3.
- >99% of circulating T3 and T4 are bound to proteins mostly thyroid binding globulin (TBG). <1 % circulates as free T3 (FT3) and free T4 (FT4).
- FT3 and FT4 enter cells, bind to intracellular receptors and activate DNA transcription to increase metabolism.
- Special situations:
    - Pregnancy: TBG increased, total T3 and T4 are increased; however, FT3 and FT4 levels are normal.
    - Cirrhosis: TBG decreased.
- Regulation:
    - Hypothalamus secretes thyrotropin releasing hormone (TRH).
    - TRH stimulates anterior pituitary to produce thyroid stimulating hormone (TSH).
    - TSH acts on follicular cells to increase secretion.
    - Both are regulated by negative feedback from T3 and T4.

10.2.1. HYPOTHYROIDISM

"It is a constellation of signs and symptoms caused by deficiency of thyroid hormone."

QUICK FACTS: HYPOTHYROIDISM	
Pathology:	**Deficiency of thyroid hormone → decreased metabolism**
Presentation:	**Fatigue, lethargy, weight gain, constipation, cold intolerance** **Bradycardia, hypertension, delayed relaxation of reflexes, dry skin, goiter**
Diagnosis:	**TSH, FT3, FT4** **Antithyroperoxidase** **Lipid profile**

	Sodium
Treatment:	**Levothyroxine replacement**

- **Primary hypothyroidism (95%):** Primary failure of thyroid gland to synthesize thyroid hormone.
- **Secondary hypothyroidism:** Deficiency of thyroid hormone due to inadequate thyroid stimulating hormone (TSH) from pituitary gland.
- **Tertiary thyroid hormone:** Deficiency of thyroid hormone due to inadequate thyrotropin releasing hormone (TRH) from hypothalamus.

- **Transient hypothyroidism:** usually resolves in some time.
- **Subclinical (mild) hypothyroidism:** minimally symptomatic patient with raised TSH but normal FT3 and FT4.
- **Clinical (overt) hypothyroidism:** symptomatic patient with raised TSH and low FT3 and FT4.

CAUSES:

- Primary: Hashimoto's thyroiditis, after hyperthyroid phase of thyroiditis, iodine deficiency, drugs (lithium, amiodarone), radio-iodine therapy, after thyroidectomy
- Secondary: pituitary disease with TSH deficiency
- Tertiary: hypothalamic disease with TRH deficiency

PRESENTATION:

A variety of features which can be divided as follows:

- Features of slowed activity/ decreased energy: weakness, weight gain, fatigue, somnolence, cold intolerance, lethargy, dyspnea on exertion, hair loss, constipation, myalgia, arthralgia, headache, hypothermia
- Metabolic derangements: increased cholesterol and triglycerides, carotenemia
- Neuropsychiatric features: hoarseness of voice, depression, psychosis (myxedema madness), slow movements, dementia, impaired concentration, impaired memory, features of carpal tunnel syndrome, cerebellar ataxia, myotonia, deafness, hyporeflexia, delayed relaxation of tendon reflexes, depression, psychosis (myxedema madness), difficulty concentrating , cerebellar ataxia
- Cardiovascular system: bradycardia, hypertension, cardiomegaly (myxedema heart)
- Accumulation of matrix: dry coarse brittle hair, dry itchy skin, brittle nails, puffy face, non-pitting edema, macroglossia
- Reproductive problems: menorrhagia, infertility, impotence
- Others: goiter, pleural effusion, pericardial effusion, ascites
- Myxedema crisis/ coma:
    - It usually occurs in elderly patients.
    - It occurs in severely hypothyroid patients.
    - It is precipitate on exposure to cold, certain drugs (sedatives, opioids, antidepressants, etc.), or on developing stroke, heart failure, infection, trauma.
    - Patients may have altered level of consciousness, convulsions, hypothermia, hypoventilation, hyponatremia, hypoglycemia, hypoxemia, hypercapnia and hypotension.
    - Mortality is very high (50 – 75%).
- Associated conditions: addison's disease, diabetes mellitus, SLE, pernicious anemia

INVESTIGATIONS:

- TSH, FT3 an FT4: see table 10.3.
- Anti-thyroperoxidase and anti-thyroglobulin antibodies
- 24-hour radio-iodine uptake: low or normal
- Lipid profile: increased LDL-C, triglycerides, lipoprotein (a),
- Others: hyponatremia, hypoglycemia, normocytic or macrocytic anemia, increased creatine kinase, prolactin, positive ANA

Table 10.3: THYROID PROFILE IN DIFFERENT DISEASES			
	TSH	**FT4**	**FT3**
Primary hypothyroidism	High	Low	Low or normal
Secondary hypothyroidism	Low or normal	Low	Low or normal
Tertiary hypothyroidism	Low TRH also low	Low	Low
Subclinical primary hypothyroidism	Low	Normal	Normal
Pregnancy (first trimester)	Low	Normal	Normal

MANAGEMENT:

- Replacement therapy: LEVOTHYROXINE (1.5-1.7 µg/kg/day in usual patients, 0.3-0.5 µg/kg/day) in early morning.
- Start with lower doses in case of concomitant addison's disease or coronary artery disease.
- Also use lower doses in elderly patients (age >60 years).
- Goal is normalization of TSH and improvement of symptoms.
- In case of myxedema crisis:
    - Warm patient with blankets.
    - Intravenous LEVOTHYROXINE 500 µg loading dose followed by 50 – 100 µg daily OR intravenous LIOTHYRONINE (T3) 10 – 20 µg loading dose followed by 10 µg every 4 – 6 hours up to 48 hours.
    - 5% dextrose for hypoglycemia.
    - Normal saline or 3% saline for hyponatremia.
    - Mechanical ventilation for hypercapnia.
    - Intravenous HYDROCORTISONE 100 mg STAT followed by 25 – 50 mg every 8 hours.

⇨ ***Hashimoto's disease is the most common cause of hypothyroidism.***

10.2.2. HYPERTHYROIDISM

"It is a condition of increased metabolism due to increased secretion of thyroid hormones."

QUICK FACTS: HYPERTHYROIDISM	
Pathology:	**Excess of thyroid hormone → increased metabolism**
Presentation:	**Nervousness, irritability, hyper-reflexia, tremors, sweating, heat intolerance Tachycardia, atrial fibrillation, hypertension, heart failure, proximal myopathy, eye signs of Grave's disease**
Diagnosis:	**Thyroid profile TSH receptor antibody (especially TSI), antithyroglobulin antibodies Thyroid scan**
Treatment:	**Antagonize action: Beta-blockers Inhibit formation of thyroid hormones: anti-thyroid medicines (methimazole, carbimazole, propylthiouracil) Definitive: Iodine-131 therapy, thyroidectomy**

PRESENTATION:

- Neuromuscular features: nervousness, insomnia, irritability, emotional lability, psychosis, hyper-reflexia, sustained clonus, proximal myopathy, hypokalemic periodic paralysis
- Features of sympathetic over-activity: hand tremor, hyperactivity, tremulousness, excessive sweating, heat intolerance
- Gastrointestinal features: weight loss despite good appetite, diarrhea, frequent defecation
- Cardiovascular system: sinus tachycardia, systolic hypertension, wide pulse pressure, palpitations, dyspnea, arrhythmias (atrial fibrillation or atrial tachycardias), ankle edema, heart failure, angina, exertional dyspnea
- Goitre:
    - Grave's disease: diffusely enlarged non-tender thyroid.

    - Sub-acute thyroiditis:
    - Multi-nodular goiter/ Hashimoto's thyroiditis:
- Features of Grave's disease:
    - Eye disease. Its spectrum can be remembered by Werner's mnemonic NO SPECS.
        - No signs or symptoms
        - Only signs of upper eye lid retraction and stare, with or without lid lag and exophthalmos e.g.
            - Von Graefe's sign: lagging of upper eyelid on downward rotation of eye
            - Kocher's sign: convulsive retraction of eyelid on fast upwards movement
            - Dalrymple's sign: widened palpebral fissure
            - Stellwag's sign: infrequent or incomplete blinking
        - Soft tissue involvement: chemosis, lid edema, conjunctival injection
        - Proptosis (measures distance from lateral orbital rim to corneal apex)
        - Extra-ocular muscle involvement which limits movements of gaze or fixes globe (usually affecting inferior or medial recti) e.g. Gifford's sign (difficulty everting upper eyelid), Möbius sign (lack of convergence), diplopia
        - Corneal involvement e.g. corneal stippling, ulceration, clouding, necrosis, perforation
        - Sight loss from optic nerve involvement as assessed by visual acuity
    - Pre-tibial myxedema
    - Thyroid bruit may be present.
    - Thyroid acropachy (clubbing)
- Others: osteoporosis, hypercalcemia, oligomenorrhea, palmar erythema, pruritis
- Thyrotoxic crisis/ storm:
    - It is presentation of severe thyrotoxicosis.
    - There is marked agitation, delirium, high fever, severe tachycardia, vomiting, diarrhea and dehydration. Patients may develop arrhythmias, heart failure or myocardial infarction.

Table 10.4: CAUSES OF HYPERTHYROIDISM
Grave's disease (most common)
Toxic multi-nodular goiter aka Plummer's disease
Toxic adenoma
Subacute De Quervain's thyroiditis
Hashimoto's thyroiditis (transiently)
Post-partum thyroiditis
Iodide-induced (supplementation, drugs e.g. amiodarone, radiographic contrasts)
Factitious
Iatrogenic (over-dose of thyroxine in hypothyroidism)
Struma ovarii
Follicular carcinoma
TSH-secreting tumors (e.g. pituitary adenoma, choriocarcinoma, hydatidiform mole)

INVESTIGATIONS:

- TSH, FT3 an FT4: see table 10.5.
- TSH-receptor antibodies especially TSIs (raised in Grave's disease)
- Other antibodies: anti-thyroglobulin, anti-thyroid peroxidase
- Thyroid scintigraphy to determine radio-active iodine uptake (RAIU) using Iodine-123 or Technetium-99m
    - Increased uptake in Grave's disease, toxic multi-nodular goiter, toxic adenoma, pituitary tumor secreting TSH, hydatidiform mole.
    - Decreased uptake in sub-acute thyroiditis, thyrotoxicosis factitia, metastatic thyroid cancer, struma ovarii.
- Thyroid ultrasound
- MRI and CT scan of orbits
- Others: hypercalcemia, deranged liver function tests, increased alkaline phosphatase, anemia, neutropenia, hypokalemia, hypophosphatemia, hypomagnesemia.

Table 10.5: THYROID PROFILE IN DIFFERENT DISEASES			
	TSH	**FT4**	**FT3**
Primary hyperthyroidism	Low	High	High
Secondary hyperthyroidism	Normal or high	High	High
Tertiary hyperthyroidism	Normal or high (TRH also high)	High	High
Subclinical primary hyperthyroidism	Low	Normal	Normal

MANAGEMENT:

- Symptomatic relief
  - Hydration
  - Beta-blockers (usually PROPRANOLOL, ATENOLOL) or calcium channel blockers (VERAPAMIL or DILTIAZEM)
- Ophthalmopathy: ophthalmologist referral, ocular lubricants, taping eyelids closed
- Anti-thyroid drug therapy – these inhibit formation and coupling of iodotyrosines in thyroglobulin. Adverse effects include agranulocytosis, aplastic anemia and hepatitis.
  - METHIMAZOLE 15 – 60 mg in three divided doses
    - It is contraindicated in first trimester.
  - PROPYLTHIOURACIL 150 – 450 mg in three divided doses
- Radio-active iodine therapy using Iodine-131
  - It is preferred in elderly patients.
  - It is contraindicated in pregnant or lactating patients.
  - It can worsen ophthalmopathy. PREDNISONE decreases this effect.
- Surgery
  - Sub-total or total thyroidectomy
  - Complications include damage to recurrent laryngeal nerve and hypoparathyroidism.

⇨ ***Grave's disease is the most common cause of hyperthyroidism.***

10.2.3. THYROID NODULES

- Palpable thyroid nodules are present in 4 – 7% of population.
- Ultrasonographically nodules may be present in 19 – 67%.
- Thyroid cancer occurs in 5 – 10% of nodules.

Table 10.6: CAUSES OF THYROID NODULES	
Adenomas	**Cysts**
Carcinomas	Simple cyst
Papillary	Cystic/ solid tumors
Follicular	**Inflammatory thyroid disorders**
Medullary	Sub-acute thyroiditis
Anaplastic	Chronic lymphocytic thyroiditis
Lymphoma	Granulomatous thyroiditis
Colloid nodule	**Dermoid**

Table 10.7: FEATURES SUGGESTIVE OF MALIGNANCY IN A THYROID NODULE
Recent or rapid growth
History of head and neck irradiation
Lymph node involvement
Symptoms of local invasion e.g. dysphagia, neck pain, hoarseness of voice
Fixation to surrounding structures
Cold nodule
Extremes of age
Male gender
Family history of thyroid cancer

APPROACH:

- If a solitary thyroid nodule is discovered on examination, then thyroid function tests should be done.
- Thyroid scan should be done in case of hyperthyroidism whereas FNAC should be done in case of euthyroid nodules. Cold nodules on thyroid scan should also undergo FNAC.
- Benign nodules should be monitored via serial examination in six months.
- Malignant nodules should undergo thyroidectomy.
- Lesions with insufficient evidence should be checked for solid or cystic components via ultrasound.
- FNAC should be repeated in case of solid components and if clinical suspicion is high then thyroid lobectomy should be done.
- Regressing cystic lesions low-risk recurrent cystic lesions should only be observed.

10.2.3. THYROID NEOPLASMS

- **Benign:** Thyroid adenoma
- **Malignant:** Papillary carcinoma, follicular carcinoma, anaplastic carcinoma, medullary carcinoma, lymphoma

⇨ ***Papillary carcinoma is the most common type of thyroid cancer.***
⇨ ***Anaplastic carcinoma is the most aggressive of thyroid cancers.***

10.2.3.1. PAPILLARY CARCINOMA

"It is a differentiated thyroid carcinoma arising from follicular cells with characteristic nuclear changes."

- Papillary carcinoma is associated with radiation exposure.

PRESENTATION:

- Asymptomatic thyroid mass (most common)
- Compression effects: cough, dyspnea, dysphagia, stridor, vocal cord paralysis.
- It tends to spread locally or via lymphatics. It may metastasize to bones and lungs.

INVESTIGATIONS:

- Thyroid function tests
- Thyroid ultrasound
- Thyroid scintigraphy with Tc99m pertechnetate or I^{131}
- Fine-needle aspiration biopsy→ psammoma bodies

TREATMENT:

- Surgical removal
- Radio-iodine therapy
- Thyroxine replacement therapy especially after total removal

10.2.3.2. FOLLICULAR CARCINOMA

"It is a differentiated thyroid carcinoma arising from follicular cells without characteristic nuclear changes of papillary carcinoma."

PRESENTATION:

- Asymptomatic thyroid mass (most common)
- Compression effects: cough, dyspnea, dysphagia, stridor, vocal cord paralysis.
- It tends to spread hematogenously and metastasizes to bone (osteolytic), lungs and CNS.

INVESTIGATIONS:

- Thyroid function tests

- Fine-needle aspiration does not differentiate well between follicular adenoma and follicular carcinoma because both have same histopathological appearance and can only be differentiated by the showing evidence of invasion into vessels and nerves.
- Thyroid ultrasound with Doppler
- Thyroid scintigraphy with Tc99m pertechnetate or I^{131}

TREATMENT:
- Surgery
- Thyroxine replacement therapy especially after total removal

10.2.3.3. ANAPLASTIC CARCINOMA

"It is an undifferentiated aggressive cancer of thyroid gland."

PRESENTATION:
- Neck mass, metastatic bone pain, compressive symptoms (dysphagia, cough, neck pain, dyspnea, etc.)

INVESTIGATIONS:
- Fine needle aspiration biopsy, open surgical biopsy

MANAGEMENT:
- Usually palliative treatment, surgcal resection with adjuvant radiotherapy and chemotehrapy

⇨ ***Anaplastic carcinoma is the most aggressive type of thyroid cancers.***

10.2.3.4. MEDULLARY CARCINOMA

"It is a cancer which develops from para-follicular or C cell of thyroid gland."

PRESENTATION:
- Neck mass,compressive symptoms, hypercalcemia (due to raised calcitonin)

ASSOCIATIONS:
- MEN syndromes

INVESTIGATIONS:
- Raised serum calcium and calcitonin

MANAGEMENT:
- Surgery, chemotherapy, radiotherapy

10.2.3.5. PRIMARY THYROID LYMPHOMA

"It is a lymphoma arising from the thyroid gland."

- These can be non-Hodgkin or Hodgkin lymphomas.

PRESENTATION:
- Rapidly growing thyroid mass with lymphadenopathy, compressive symptoms
- They can arise in pre-existing Hashimoto's thyroiditis.

INVESTIGATIONS:
- Histopathology, CBC, LDH, thyroid function tests

MANAGEMENT:

- Chemotherapy, radiotherapy

10.3. DISEASES OF PARATHYROID GLAND

- PTH activates osteoclasts resulting in bone resorption.
- PTH inhibits proximal tubular absorption of phosphate.
- PTH increases calcium resorption from distal tubule.
- PTH stimulates 1-α-hydroxylase which increases vitamin D activation. Vitamin D in turn leads to increased dietary absorption of calcium.

10.3.1. HYPOPARATHYROIDISM

"Hypoparathyroidism is a condition of parathyroid deficiency."

QUICK FACTS: HYPOPARATHYROIDISM	
Pathology:	**Deficiency of PTH → inadequate maintenance of calcium in blood**
Presentation:	**Numbness and tingling in mouth, toes and fingers, irritability, anxiety, mood swings, seizures, laryngospasm** **Hyperactive reflexes, Chvostek's sign, Trousseau's sign, muscle cramps, tetany**
Diagnosis:	**Low calcium, high phosphorus, low PTH**
Treatment:	**Calcium supplementation, vitamin D replacement** **Recombinant PTH**

Table 10.8 : CAUSES OF HYPOPARATHYROIDISM

Iatrogenic	(Most common cause in developing countries) Post-thyroidectomy Post-parathyroidectomy Post-irradiation of head and neck
Autoimmune	Autoimmune hypoparathyroidism (most common cause in developed countries) Type 1 polyglandular syndrome
Congenital	DiGeorge syndrome Fetal alcohol syndrome Kearns-Sayre syndrome and other genetic causes
Metabolic	Hemochromatosis Wilson's disease Thalassemia Hypermagnesemia or hypomagnesemia Aluminum toxicity
Infiltrative	Metastases Granulomatous disease Amyloidosis Syphilis

- **Primary hypoparathyroidism:** Disease of parathyroid gland → inadequate PTH → hypocalcemia
- **Secondary hypoparathyroidism:** Hypercalcemia → low PTH
- There is a G-protein coupled extracellular calcium-sensing receptor in parathyroid glands which responds to calcium concentration in plasma. It regulates the secretion of parathyroid hormone (PTH). Hypocalcemia increases secretion of PTH which acts on bones and kidneys to restore calcium concentration. Hypercalcemia has the inverse effect.
- **Pseudohypoparathyroidism (PHP):**
- There is GNAS1 mutation due to which there is normal PTH receptor but defective post-receptor mechanism.
- It has five variants. PHP 1a is also known as Albright's hereditary osteodystrophy (AHO). It is the most common variant in which there is short stature, short 4th metacarpal and metatarsal, rounded face, obesity, subcutaneous calcification, developmental delay, dental hypoplasia and soft tissue calcification.

Table 10.9: TYPES OF HYPOPARATHYROIDISM							
	Ca	Phos	Alk Phos	PTH	25-OH D	1,25-OH D	Others
Hypo-parathyroidism	↓	↓	-	↓	↓	N/↓	u. cAMP ↓
Pseudo-hypo-parathyroidism 1A	↓	↑	-	↑	N	↓	Albright's hereditary osteodystrophy +
Pseudo-hypo-parathyroidism 1B	↓	↑	-	↑	N	↓	
Pseudo-hypo-parathyroidism 1C	↓		-	↑			Albright's hereditary osteodystrophy +
Pseudo-hypo-parathyroidism 2	↓	↑	-	↑	N	↓	
Pseudo-pseudo-hypo-parathyroidism	N	N	-	N/↑	N	N	Albright's hereditary osteodystrophy +

PRESENTATION:

Symptoms: mainly due to hypocalcemia

- Paresthesias in form of numbness and tingling especially around mouth, and in fingers and toes; hyper-irritability, fatigue, anxiety, mood swings, personality changes, grand mal seizures, hoarseness of voice (due to laryngospasm), wheezing and dyspnea (due to bronchospasm), muscle cramps especially of lower back, legs and feet; sweating; biliary colic.

Signs:

- **Due to hypocalcemia:**
  - Hyperactive deep tendon reflexes
  - Chvostek's sign (Twitching of ipsilateral facial muscles on tapping of facial nerve)
  - Trousseau's sign (Development of carpopedal spasm by inflating a BP cuff around arm at a pressure of 20 mmHg above the systolic BP, for more than three minutes)
  - Muscle cramps, tetany, laryngospasm, bronchospasm; paraplegia; ataxia; dysphagia; dysarthria; papilledema; prolonged QT interval, congestive heart failure.
  - Psychiatric features due to hypocalcemia: emotional instability, anxiety, depression, confusion, hallucinations.
- **Chronic hypocalcemia:** cataracts; abnormal dentition; dry, puffy and coarse skin, candida infections.
- **Due to basal ganglia calcifications in primary hypoparathyroidism:** Choreathetoid movements

INVESTIGATIONS:

- PTH levels: inappropriately low (elevated in pseudohypoparathyroidism)
- Calcium levels: low (high in secondary hypoparathyroidism)
- Phosphorus levels: high
- Urinary cAMP: low
- ECG: prolonged QT interval
- Brain imaging: basal ganglia calcifications
- Also check serum albumin, total protein levels, serum magnesium, vitamin D level, pH (for alkalosis)

TREATMENT:

- Calcium-rich diet e.g. almonds, legumes, leafy green vegetables, oats, sardines, apricots, coconut meat, onions, pumpkin seeds
- Replace oral or iv calcium depending on the severity of symptoms. Keep calcium level at 8.0 – 8.5 mg/dl (higher levels can lead to renal stones).
  - Give 100 mg of elemental calcium iv over 10 – 20 minutes
    - 10 ml of 10% injectable calcium chloride = 1000 mg calcium chloride = 363 mg elemental calcium = 9.07 mmol of calcium = 13.6 mEq of calcium
    - 10 ml of 10% injectable calcium gluconate = 1000 mg calcium gluconate = 93 mg elemental calcium = 2.2 mmol of calcium = 4.65 mEq of calcium

    - 500 – 1500 mg oral calcium gluconate daily in divided doses
    - 1250 mg oral calcium carbonate two to three times daily with meals
- Calcium is needed for life-time
- Give active vitamin D (calcitriol)
- During treatment with calcium and vitamin D, watch for development of renal stones.
- Recombinant human parathyroid hormone (rhPTH) or TERIPARATIDE
- Replace magnesium if hypomagnesemia
- Auto-transplantation of parathyroid gland in patients undergoing parathyroidectomy.

Table 10.10: TYPES OF OSTEOMALACIA

	Ca	Phos	Alk Phos	PTH	25-OH D	1,25-OH D	Urine studies	Others
Vitamin D deficiency	**N/ ↓**	**N/ ↓**	↑	↑	↓	↓/↑	**u. PO4 ↑ u. Ca N/↑**	Aminoacids ↑
Hypocalcemic rickets	↓		↑	↑	**N**	↑	**u. PO4 N/↑ u. Ca ↓**	**-**
Vitamin D dependent rickets type 1	**N/↓**	↓	↑	↑	**N/↑ (1a) ↓↓ (1b)**	**↓↓ (1a) Variable (1b)**	**u. PO4 ↑ u. Ca ↓**	**-**
Vitamin D dependent rickets type 2	↓	↓	↑	↑	**N/↑**	↑↑	**u. PO4 ↑ u. Ca ↓**	**-**
Vitamin D resistant rickets type 1	**N/ ↓**	↓	↑	↑	**N**	↓	**u. PO4 ↑ u. Ca N/↓**	**FGF23 ↑**
Vitamin D resistant rickets type 2	**N/ ↓**	↓	↑	↑	**N**	↑	**u. PO4 ↑ u. Ca N/↓**	**FGF23 ↑**
Hypophosphatasia	↑	↑	↓↓	↑	↑	↑	**u. PO4 N/↓ u. Ca ↓**	**-**
Hyperparathyroidism	↑	↓	↑	↑				**u. cAMP ↑**
Renal osteodystrophy	↓	↑	**N/↑**	↑	**N/↓**	↓↓	**u. PO4 N/↓ u. Ca N/↑**	**-**

10.3.2. HYPERPARATHYROIDISM

"Hyperparathyroidism is a condition of parathyroid hormone over-production."

- **Primary hyperparathyroidism:** It is unregulated over-production of PTH from disease of parathyroid gland itself.
- **Secondary hyperparathyroidism:** It is overproduction of PTH due to a chronic abnormal stimulus e.g. hyperphosphatemia, hypocalcemia and hypovitaminosis D of renal failure.
- **Tertiary hyperparathyroidism:** autonomous production of PTH after secondary parathyroidism

10.3.2.1. PRIMARY HYPERPARATHYROIDISM

QUICK FACTS: PRIMARY HYPERPARATHYROIDISM	
Pathology:	**Excess PTH → excessive bone resorption and calcium retention**
Presentation:	**Flank pain, dysuria, bone pain, pathologi fractures, depression, pancreatitis, proximal myopathy**
Diagnosis:	**High calcium, low phosphorus, high PTH**
Treatment:	**Surgical resection** **Correct hypocalcemia** **Cinacalcet**

CAUSES:
- Adenoma (85%) – mostly right inferior parathyroid
- Hyperplasia (15%)
- Carcinoma (<1%)

SYMPTOMS:
- Due to renal stones/ nephrocalcinosis: loin pain, dysuria (most common presentation)
- Due to bone resorption (selective cortical loss): bone aches, bone pains, osteoporosis, pathologic fractures
    - Osteitis fibrosa cystica (brown tumor or osteoclastoma): generalized increase in osteoclastic bone resorption especially from phalanges, tooth sockets and skull (salt-and-pepper appearance) and replacement by fibrous tissue. These lesions appear as lytic lesions on x-rays.
- Due to hypercalcemia: symptoms of pancreatitis, peptic ulcer disease, gout; constipation; muscle pain and proximal myopathy; polydipsia; polyuria; hypertension (diastolic); weight loss, anorexia, nausea, vomiting; chondrocalcinosis
- Psychiatric features: depression; fatigue; anorexia; sleep disturbances; inability to concentrate

INVESTIGATIONS:
- Serum calcium levels and levels corrected for albumin OR ionized calcium levels: high
- PTH: high in relation to hypercalcemia
- Phosphate level: low
- Urinary calcium level: raised
- Urinary phosphate: raised
- Urinary cAMP: raised
- Bicarbonate level: low (non-gap acidosis due to RTA-2)
- Chloride:phosphate ratio>33 (<29 excludes primary hyperparathyroidism)
- Radio-labeled Technetium-99m sestamibi scan: uptake in thyroid and parathyroid glands initially but later washout from thyroid

MANAGEMENT:
- Surgical resection
- Treatment of hypocalcemia and hypovitaminosis D

- Calcimimetics: CINACALCET
- Avoid diuretics, thiazides and lithium
- Bisphosphonates, SERMs or estrogen replacement for osteoporosis

⇨ ***Symptoms of primary hyperparathyroidism are remembered by the mnemonic: Bones, stones, abdominal groans, moans and psychic overtones.***

10.3.2.2. SECONDARY HYPERPARATHYROIDISM

QUICK FACTS: SECONDARY HYPERPARATHYROIDISM	
Pathology:	**Low vitamin D or low calcium or high phosphate →Excess PTH → excessive bone resorption and calcium retention**
Presentation:	**Osteoporosis, osteomalacia, fractures, myopathy, pruritis, cardiovascular calcification** **Featurs of underlying cause**
Diagnosis:	**Low calcium, high phosphorus, high PTH** **Low vitamin D**
Treatment:	**Sunlight exposure, replace vitamin D, calcium supplements** **Parathyroidectomy in severe cases** **Cinacalcet**

PATHOGENESIS:
- Hypovitaminosis D, hypocalcemia and hyperphosphatemia → hyperplasia of parathyroid glands

CAUSES:
- Renal failure (stage IV and V)
- Stomach or intestine bypass surgery
- Celiac disease
- Crohn's disease
- Severe vitamin D deficiency

PRESENTATION:
- Osteoporosis, osteomalacia, fractures, myopathy
- Pruritis (calcium and phosphorus deposition in skin)
- Cardiovascular calcification
- Left ventricular hypertrophy
- Calciphylaxis (calcification of small arterioles and venules with intimal hyperplasia)

INVESTIGATIONS:
- Calcium, phosphorus, vitamin D, intact PTH

MANAGEMENT:
- Sunlight exposure (if lacking)
- For hypovitaminosis D: 400 IU of vitamin D2 (ergocalciferol) or D3 (cholecalciferol) daily
- For renal failure:
    - Target PTH levels are:35 – 70 pg/ml (stage 3), 70 – 110 pg/ml (stage 4), 150 – 300 pg/ml (stage 5). If PTH high:
        - Treat hyperphosphatemia:
            - Keep phosphorus 2.7 – 4.6 mg/dl (stage 3 – 4) or 3.5 – 5.5 mg/dl (stage 5)
            - Restrict dietary phosphorus to 800 – 1000 mg/day.
            - Give phosphate binders if dietary restrictions fail
                - Calcium-based phosphate binders e.g. CALCIUM ACETATE 1 – 4 capsules (667 mg) with each meal
                - Non-calcium based phosphate binders: SEVELAMER 800 – 1600 mg thrice daily or LANTHANUM 1500 – 4500 mg daily in three divided doses
        - Give calcitriol or vitamin D analogs.

        - In stage 3 – 4, vitamin D supplementation even if vitamin D levels >30 ng/ml to decrease PTH. In stage 5, vitamin D supplementation to keep PTH in target range.
            - If vitamin D level <30 ng/ml, give ergocalciferol or cholecalciferol
            - If vitamin D level >30 ng/ml, then check if calcium <9.5 mg/dl, phosphorus <5.5 mg/dl and Ca x P product <55 mg2/dl2. If yes, then give calcitriol.
                - 0.25 µg/day (for PTH 70 – 300 pg/ml in stage 3 or PTH 110 – 300 pg/ml in stage 4)
                - 0.5 – 1.0 µg/day (PTH 300 – 600 pg/ml)
                - 1 – 2 µg/day (600 – 1000 pg/ml)
        - Cinacalcet if all above fails.
    - Target calcium levels are between 8.4 – 9.5 mg/dl. Give calcium supplements (keep total dietary calcium <2 g/day) if calcium <8.4 mg/dl or PTH >55 pg/ml. Also maintain serum calcium-phosphorus product at <55mg2/dL2 in adults.
    - Discontinue calcium supplementsif serum calcium >9.5 mg/dl or PTH below target. Avoid calcium-based phosphate binders or vitamin D. keep serum calcium x phosphate product <55mg2/dl2.
    - Vitamin D therapy
        - During stage 1 – 2: give vitamin D only if vitamin D level <30 ng/ml.
        - During stage 3 – 4: give vitamin D even if vitamin D level >30 ng/ml but PTH higher than target.
        - During stage 5: give vitamin D to keep PTH in between 150 – 300 ng/L.
    - Parathyroidectomy in case of severe hyperparathyroidism.
    - Calcimimetic therapy: CINACALCET binds to calcium-sensing receptor on parathyroid glands and decreases PTH by negative feedback.

10.3.2.3. TERTIARY HYPERPARATHYROIDISM

PATHOGENESIS:

- Long-standing secondary hyperparathyroidism → parathyroid glands become autonomous → calcium becomes normal or raised

PRESENTATION:

- Calcium level becomes normal or raised
- Persistent hyperparathyroidism after renal transplantation

MANAGEMENT:

- Total parathyroidectomy with auto-transplantation
- Sub-total parathyroidectomy

10.4. DISEASES OF PANCREAS

10.4.1. DIABETES MELLITUS

"It is a complex metabolic disorder characterized by hyperglycemia (glucose intolerance) resulting from relative or absolute deficiency of insulin."

QUICK FACTS: DIABETES MELLITUS	
Pathology:	**Type 1: Autoimmune destruction of beta cells → deficiency of insulin → hyperglycemia** **Type 2: elevated FFA → insulin resistance, dysfunction of beta cells, increased gluconeogenesis, increased mobilization of fatty acids** **Consequences of diabetes: oxidative stress, advanced glycation products, etc.**
Presentation:	**Polydispisa, polyuria, polyphagia, weight loss or gain, DKA** **Microvascular complications: retinopathy, nephropathy, neuropathy** **Macrovascular complications: coronary artery disease, peripheral vascular disease and other atherosclerotic arterial diseases** **Acute complications: hypoglycemia, DKA, HHS** **Others: cataracts, glaucoma, frequent infections, foot ulcers**
Diagnosis:	**FBS, OGTT, HbA1C (FBS ≥126 mg/ dL, 2-hour post prandial ≥180 mg/dL, HbA1C ≥6.4%)** **C-peptide, insulin levels**
Treatment:	**Life-style changes** **Oral hypoglycemic drugs (Insulin sensitizers: biguanides. Secretagogues: sulfonylureas, meglinitides. Incretins: DDP4 inhibitors, GLP-1 agonists. Glycosuric drugs: SGLT2 inhibitors. Alpha glucosidase inhibitors, amylinomimetics, short-release bromocriptine)** **Insulins and insulin analogues** **Continuous subcutaneous insulin infusion (CSII)**
Targets:	**FBS or pre-prandial: 80 – 130 mg/dL (ADA) <110 mg/ dL (AACE)** **2-hour post prandial: 80 – 180 mg/dL (ADA) <140 mg/ dL (AACE)** **HbA1C: <7% (most), <6.5% (young adults), <8% (elderly and those with comorbids)**
Monitoring:	**Screen for retinopathy: after 5 years in T1DM then annual , STAT in T2DM then annual** **Screen for nephropathy: after 5 years in T1DM then annual , STAT in T2DM then annual** **Screen for neuropathy: after 5 years in T1DM then annual , STAT in T2DM then annual** **Screen for diabetic foot: annually and at every visit**

TYPES OF DIABETES AND PATHOPHYSIOLOGY:

- **Type 1 Diabetes** is characterized by ß-cell destruction, absolute insulin deficiency and a tendency to develop ketosis.
    - Autoimmune destruction of ß-cells proteins e.g. islet cell antibodies or anti-insulin antibodies.
    - Absence of insulin → decreased glucose transport to muscles and fat cells → excessive or inappropriate glucagon secretion → elevated hepatic glucose production especially gluconeogenesis.
    - Loss of inhibition of hormone-sensitive lipase → increased mobilization of fatty acids and triglycerides from fatty tissues → can lead to keto-acidosis.
- **Type 2 Diabetes** is characterized by insulin resistance, progressive insulin secretory defect and excessive hepatic glucose generation.
    - Elevated free fatty acids and pro-inflammatory cytokines → peripheral insulin resistance
    - ß-cells are desensitized (genetic defects, chronic hyperglycemia or increased free fatty acids) → inappropriate insulin secretion. (In pre-diabetes states, the ß-cells are able to

compensate for hyperglycemia. In diabetes, there is failure to secrete enough insulin in response to hyperglycemia).
    - Decreased glucose transport to muscles and fat cells → excessive or inappropriate glucagon secretion → elevated hepatic glucose production especially gluconeogenesis.
    - Loss of inhibition of hormone-sensitive lipase → increased mobilization of fatty acids and triglycerides from fatty tissues.
- **Gestational Diabetes (GDM)** is the onset of glucose intolerance which is recognized first during second or third trimester of pregnancy and is not clearly overt diabetes.
    - It is almost the same as type 2 diabetes mellitus however insulin ressitance and beta cell dysfunction are also contributed by placental hormones.
- **Other specific diabetes types:** see table 10.11
- Other important related conditions include:
    - **Pre-diabetes:** These are individuals who are at increased risk for development of diabetes and include individuals with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or impaired glycosylated hemoglobin A1c (HbA1c).
    - **Metabolic syndrome:** It is a group of metabolic derangements that is associated with a high risk of cardiovascular disease. It is characterized by:
        - Abdominal obesity (Waist circumference >102 cm in men and >88 cm in women)
        - Atherogenic dyslipidemia (TG ≥150 mg/dl; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women)
        - Raised blood pressure (≥130/85 mmHg)
        - Insulin resistance (Fasting glucose ≥100 mg/dl
        - Others: hyperinsulinemia, increased LDL-cholesterol, microalbuminuria, increased high sensitivity CRP, increased uric acid, increased fibrinogen, non-alcoholic fatty liver, polycystic ovarian syndrome (in women).

CONSEQUENCES OF DIABETES:

Chronic hyperglycemia leads to following hyperglycemia-mediated damage to endothelial cells, renal mesangial cells, neurons and Schwann cells leading to generation of reactive oxygen species. This occurs by means of:

- Polyol pathway: generation of excessive sorbitol and depletion of NADPH thus reducing ability to fight oxidative stress.
- Glycation of proteins and lipids: leading to generation of advanced glycation end-products (AGEs) which affects their function and also activate inflammatory cytokines.
- Others: like activation of protein kinase C, hexosamine pathways, osmotic damage, etc.

PRESENTATION:

- Usually asymptomatic
- Classically polyuria, polydipsia, polyphagia, weight loss or weight gain, fatigue, weakness, blurred vision, frequent superficial infections (especially candidal infections like thrush or vaginitis), tingling sensations in hands and feet, and poor wound healing.
- Other features may include frequent genitourinary, oral or dermatologic infections, reactive hypoglycemia or acanthosis nigricans.
- Type 2 diabetics lack overt symptoms and often present late.
- Type 1 diabetics may sometimes present with diabetic ketoacidosis (DKA).
- Complications of disease
- Associated conditions: hypothyroidism, addison's disease, vitiligo etc.

Table 10.11: OTHER SPECIFIC DIABETES TYPES	
Genetic defects in ß-cell function	Maturity-Onset Diabetes of Young (MODY 1-6) Mitochondrial DNA
Genetic defects in insulin action	Type A insulin resistance Leprechaunsim Rabson-Mendenhall syndrome Lipoatrophic diabetes
Infrequent autoimmune causes	Stiff-man syndrome Antibodies against insulin receptors
Diseases of exocrine pancreas	Pancreatitis Pancreatic neoplasia Cystic fibrosis Pheochromocytoma Trauma Hemochromatosis
Endocrinopathies	Acromegaly Cushing syndrome Glucagonoma Pheochromocytoma Hyperthyroidism MEN-1
Drug- or chemical-induced diabetes	Glucocorticoids Thiazides Diazoxide Pentamidine Dilantin Nicotinic acid
Infections	Congenital rubella Cytomegalovirus
Other syndromic associations	Down syndrome Klinefelter syndrome Turner syndrome Wolfram syndrome Lawrence-Moon-Biedel syndrome Friedreich ataxia Huntington's chorea Myotonic dystrophy Porphyria Prader-Willi syndrome

Table 10.12: COMPARISON OF TYPE 1 AND TYPE 2 DIABETES		
	Type 1 diabetes	**Type 2 diabetes**
Age of onset	Usually younger (<30 years)	Usually older (>30 years)
Presentation	Usually present with classical symptoms or DKA	Usually asymptomatic
Duration of symptoms	Weeks	Months to years
Weight	Usually thin lean	Usually obese
Family history of diabetes	Uncommon	Common
Complications	Usually develop later after diagnosis	Usually present at or soon after diagnosis
Ketonuria	Present	Usually absent
Autoantibodies	Mostly present	Not present
Outome without insulin	Death may occur	Slow development of complications, usually rapid death does not occur
Associations	Other autoimmune diseases	Other cardiovascular comorbids e.g. hypertension, metabolic syndrome

COMPLICATIONS:

Acute:

- Hypoglycemia
- Diabetic ketoacidosis (DKA)
- Hyperglycemic hyperosmolar state (HHS) or hyperosmolar hyperglycemic non-ketotic syndrome (HHNS)

Chronic:

- Microvascular complications:
    - Diabetic eye disease or retinopathy
    - Diabetic kidney disease

    - Neurologic
        - Distal symmetric neuropathy
        - Cranial neuropathy
        - Mono-neuropathy
        - Autonomic neuropathy
- Macrovascular complications:
    - Coronary artery disease
    - Cerebrovascular disease
    - Peripheral vascular disease
- Feto-maternal complications:
    - Maternal: pre-eclampsia, diabetic ketoacidosis, pre-term labor, polyhydramnios, need for C-section due to macrosomia
    - Fetal: macrosomia, birth defects, birth injury, neonatal hypoglycemia, peri-natal mortality
- Others:
    - Cardiomyopathy (usually dilated but sometimes restrictive)
    - Diabetic foot disease
    - Limb gangrene and amputations
    - Early cataracts
    - Glaucoma
    - Frequent infections and immunosuppression
    - Depression
    - Diabetes-related cognitive dysfunction and dementia

Table 10.13: CRITERIA FOR DIAGNOSIS OD PRE-DIABETES AND DIABETES
(The tests should be confirmed by a repeat test on a different day unless unequivocal hyperglycemia is present)

	PRE-DIABETES	DIABETES
Fasting blood sugar	100-125 mg/dl (5.6-6.9 mmol/l)	≥126 mg/dL (≥7.0 mmol/L)
2-hour post-prandial glucose (in standard glucose tolerance test performed using a glucose load of 75 g anhydrous glucose)	140-199 mg/dl (7.8-11.1 mmol/l)	≥200 mg/dL (≥11.1 mmol/L)
HbA1c	5.7-6.4% DCCT/NGSP (38.8 – 48 mmol/mol IFCC)	≥6.5% DCCT/NGSP (>48mmol/mol IFCC)
Random blood sugar (with classic symptoms or presenting with hyperglycemic crisis)	-	≥200 mg/dl (≥11.1 mmol/l)

INVESTIGATIONS:

- Diagnostic tests: fasting blood sugar, random blood sugar, oral glucose tolerance test, HbA1c, urinary glucose
- C-peptide: can be used to differentiate type 1 and 2 diabetes. It is raised in type 2 diabetes whereas it is absent or low in type 1.
- Monitoring tests: fasting blood sugar, 2-hour post prandial blood sugar, HbA1c
    - HbA1c is a form of hemoglobin which has bound to glucose as a result of slow glycation. It is not only diagnostic of diabetes but also indicates glucose control over last three months.
- Fasting lipid profile: raised triglycerides, LDL-cholesterol and low HDL-cholesterol.
- Tests for screening and diagnosis of complications:
    - Nephropathy: urine detailed report for proteinuria, urine protein:creatinine ratio, 24-hour urine protein, creatinine, ultrasound for kidney size and parenchymal changes
    - Neuropathy: detailed neurological examination, nerve conduction studies
    - Retinopathy: ocular examination, visual acuity, dilated retinal examination, fundus photography
    - Coronary artery disease: ECG, stress tests, coronary angiography, echocardiography
    - Peripheral arterial disease: pulses examination, blood pressure, ankle-brachial index, ultrasound arterial doppler study, peripheral angiography
    - Cerebrovascular disease: dementia screening and neurological examination, CT scan or MRI brain.

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$$\textbf{Estimated Average Glucose or eAG } \left(\frac{mg}{dL}\right) = (28.7 \times HbA1c) - 46.7$$

SCREENING FOR DIABETES:

Screen following persons ***every three years*** for risk of diabetes:

1. Age >45 years
2. Age <45 years but having BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans and at least one of the following risk factors
    a. First degree relative with DM
    b. Physical inactivity
    c. High-risk race/ ethnicity
    d. Women with a macrosomic baby (weight >9 lb) or history of GDM
    e. Hypertension
    f. HDL cholesterol <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)
    g. Polycycstic ovarian syndrome
    h. HBA1C ≥5.7% or having IFG or IGT (***Screening should be done every year***)
    i. Clinical conditions associated with insulin resistance e.g. acanthosis nigricans.
    j. History of vascular disease

Test using fasting blood glucose, random blood glucose, oral glucose tolerance test or glycated hemoglobin A1c. If the test is normal then repeat at least on a 3-yearly basis. Pre-diabetics should be screened annually. In children screening should begin at age of ten years or at onset of puberty.

MANAGEMENT:

- Management of diabetes starts with life-style advice. Type 1 diabetics urgently require insulin from the beginning while type 2 diabetics are started on metformin or other oral hypoglycemic drugs. Patients with advanced type 2 diabetes also require insulin.

General management:

- Overweight/ obesity:
    - Maintain optimal weight and manage obesity. Use of ORLISTAT, LORCASERIN, PHENTERMINE/ TOPIRAMATE ER, NALTREXONE/ BUPROPION, LIRAGLUTIDE or bariatric surgery as needed.
- Diet:
    - Calories restriction
    - Prefer plant-based diet
    - Avoid trans-fatty acids in diet. Take polyunsaturated and monounsaturated fatty acids. Limit saturated fatty acids.
    - Decrease intake of animal fats and refined carbohydrates
    - Take high-fiber diet
    - Take fruits, vegetables and whole grains.
- Physical activity:
    - Perform at least 150 minutes per week of moderate-intensity aerobic exercises e.g. brisk walking, climbing stairs OR at least 90 minutes of vigorous aerobic exercises per week.
    - Do resistance training exercises if not able to perform aerobic exercises.
- Sleep:
    - Sleep hygiene and at least 7 hours of sleep.
    - Screen for obstructive sleep apnea.
- Smoking and alcohol cessation.
- Behavioral support
- Modify risk factors for atherosclerotic cardiovascular disease.
    - Treat dyslipidemia
        - All diabetic patients ≥ 40 years of ageshould receive statins. Patients <40 years should receive statins if having clinical ASCVD or high risk of ASCVD.
        - All patients should follow life-style changes.
        - Reduce saturated fat, trans-fat and cholesterol intake. Increase n-3 fatty acids, fibers and plant-based fats.
        - Lower LDL-cholesterol to <70 using statins. Add EZETIMIBE or PCSK9 inhibitors if needed.

        - If triglycerides >500 mg/dL: add fibrates, omega-3 fatty acids or niacin.
    - Treat hypertension
        - Goal of treatment is a BP<130/80 mmHg.
        - Use ACE inhibitor or ARB as the first option.
        - If needed then add calcium channel blocker, beta-blocker or thiazide and keep adding from these till goal achieved.
        - If goal still not achieved then add other agents.
    - Ischemc heart disease:
        - Aspirin is recommended for secondary prevention or for primary prevention in patients with high risk.
        - Patients may not develop chest pain and the disease may be silent.
- Screening for complications
- Foot care: inspect whole of feet daily; clean feet gently daily; apply moisturizers; avoid hot soaks/ heating pads; trim toe-nails instead of cutting them; wear clean socks and comfortable shoes; do not wear new hard shoes or leather shoes continuously from beginning; use a mirror to view under-surface of feet; inform doctor in case of wound or cut on feet.

Table 10.14: SCREENING FOR COMPLICATIONS IN DIABETES

Complications	Screening recommendations	Screening tests	Preventive measures
Diabetic kidney disease	Start in type-1 diabetes of ≥ 5 years duration, type-2 diabetes at diagnosis and all patients with comorbid hypertension. Thereafter screen annually.	Urinary albumin-to-creatinine ratio 24-hour urinary protein Creatinine and estimated GFR	Optimize glucose and BP control ACEI or ARB
Diabetic eye disease	Start in type-1 diabetes of ≥ 5 years duration, type-2 diabetes at diagnosis and all pregnanct females. Thereafter screen every 1 – 2 years if no disease, every year if retinopathy. Screen more frequently if progressive or sight-threatening disease or pregnant.	Dilated fundus exam Retinal photography	Optimize glucose, BP and lipid control Prompt referral to ophthalmologist
Diabetic neuropathy	Start in type-1 diabetes of ≥ 5 years duration and type-2 diabetes at diagnosis. Thereafter screen annually.	Neurological exam including temperature, pin-prick and vibration sense and 10-gram monofilament test. Nerve conduction studies	Optimize glucose control.
Diabetic foot disease	Annually and at every visit.	Comprehensive foot evaluation and assessment of risk factors Podiatrist visit Assess vascular supply Ankle-brachial index	Optimize glucose control. Diabetic foot care education. Stop smoking. Special foot-wear in high-risk patients.
Cardiovascular risk assessment	Fasting lipid profile: annually if normal, every 3 months if elevated Blood pressure: every 3 months Body weight: every 3 months	Relevant tests	Optimize glucose, BP and lipid control Life-style changes
Depression	Annual screening	Psychiatric interview	Healthy life-style, diabetes education
Dental and peri-odontal disease	Every six months	Dentist exam	Optimize glucose control Dental hygiene

HYPOGLYCEMIA AWARENESS:

- Explain symptoms of hypoglycemia. Tell about alert level of ≤70 mg/dL.
- Ask about episodes of hypoglycemia.
- Take 15 – 20 g of glucose if experience hypoglycemia.
- Prescribe glucagon for patients at high risk of hypoglycemia.

PHARMACOLOGICAL TREATMENT:

- Use pharmacological therapy if life-style modifications fail. If HbA1c target not achieved after 3 months then upgrade current therapy.
- Type-1 diabetes: Treatment of choice is insulin usually in a basal-bolus regime in which a long-acting insulin is given along with rapid-acting insulins before meals. Pramlintide can be used to decrease insulin dose and to induce weight loss. Metformin can reduce insulin requirements but has no improvement in glycemic control. GLP-1 agonists and DPP-4 inhibitors are being studied. Novel treatments include pancreatic or islet transplantation.
- Type-2 diabetes: METFORMIN is the drug of choice unless contraindicated or not tolerated. Start monotherapy with METFORMIN unless HbA1c ≥9% in which case consider dual or triple therapy with consideration for insulin. Consider initiating insulin if entry HbA1c ≥10% and/or blood glucose ≥300 mg/dL. Choice of drugs is also guided by efficacy, risk of hypoglycemia, effect on weight, history of atherosclerotic cardiovascular disease, side-effects, renal effects, delivery method, cost and patient preference.

<u>ORAL HYPOGLYCEMIC:</u>

Insulin sensitizers:

- Biguanides: METFORMIN
  - It is the drug of choice for type 2 diabetes.
  - Effects: increases insulin sensitivity, decreases gluconeogenesis.
  - Advantages: high efficacy, low risk of hypoglycemia, promotes weight loss, low cost, potential benefit in ASCVD, neutral effect in progression of CHF and CKI.
  - Side-effects: gastrointestinal symptoms (nausea, diarrhea), B12 deficiency, metformin – associated lactic acidosis (MALA).
  - Dose: METFORMIN 500 – 2550 per day in divided doses during or immediately after meals.
  - Contrary to popular belief, metformin does not cause renal failure nor is it contraindicated in renal failure. It can be used in renal failure if the GFR is >30 ml/min.
- Thiazolidinediones:
  - Effects: bind to peroxisome proliferator-activated receptor gamma in adipocytes and promote fatty acid uptake in peripheral fat.
  - Advantages: high efficacy, low risk of hypoglycemia
  - Side effects: weight gain, congestive heart failure, edema, risk of bone fractures
  - Examples: ROSIGLITAZONE, PIOGLITAZONE

Insulin secretagogues:

- Sulfonylureas:
  - Effects: block potassium channels on pancreatic ß-cells and stimulate insulin release.
  - Advantages: high efficacy, low cost
  - Side effects: hypoglycemia, weight gain, increased cardiovascular mortality in first generation drugs
  - Examples:
    - First generation: TOLBUTAMIDE, TOLAZAMIDE, CHLORPROPAMIDE, ACETOHEXAMIDE
    - Second generation: GLIPIZIDE, GLYBURIDE (GLIBENCLAMIDE), GLICLAZIDE
    - Third generation: GLIMEPIRIDE
- Meglitinides/ glinides:
  - Effects: block potassium channels on pancreatic ß-cells and stimulate insulin release.
  - Side effects: weight gain, small risk of hypoglycemia
  - Examples: NATEGLINIDE, REPAGLINIDE

Incretins: these are hormones secreted by digestive tract in response to glucose load and enhance insulin release as well as inhibit glucagon. These include glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

- Dipeptidyl peptidase-4 (DPP-4) inhibitors or Gliptins:
  - Effects: inhibit DPP-4 and prevent degradation of incretins.
  - Advantages: low risk of hypoglycemia, weight neutral.
  - Side effects: pancreatitis, joint pain, flu-like symptoms, skin reactions.
  - Examples: SITAGLIPTIN, VILDAGLIPTIN, SAXAGLIPTIN, LINAGLIPTIN
- Glucagon-like peptide-1 (GLP-1) receptor agonists:
  - Effects: act like GLP-1.
  - Advantages: high efficacy, low risk of hypoglycemia, promote weight loss
  - Side effects: GI symptoms (nausea, vomiting, diarrhea), injection site reactions, risk of pancreatitis, risk of thyroid C-cell tumors

- Examples: EXENATIDE, LIXISENATIDE, DULAGLUTIDE, LIRAGLUTIDE

Glycosuric drugs:

- SGLT2 inhibitors:
  - Inhibit sodium-glucose contransporter 2 in proximal renal tubule preventing glucose re-absorption. These agents thus provide an insulinindependent lowering of glucose.
  - These are not used in type-1 diabetes or advanced renal failure.
  - Advantages: low risk of hypoglycemia, promote weight loss
  - Side-effects: candida infections, ketoacidosis, urinary tract infections, risk of amputation and bone fractures.
  - Examples: CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN

Others

- Alpha glucosidase inhibitors:
  - Prevent digestion of carbohydrates, delay sugar absorption and help prevent post-prandial glucose surges.
  - Advantages: low risk for hypoglycemia, weight neutral
  - Side effects: flatulence, diarrhea
  - Examples ACARBOSE, MIGLITOL, VOGLIBOSE
- Amylinomimetics:
  - It is an amylin analog used in type-1 diabetes.
  - It delays gastric emptying, blunts pancreatic secretion of glucagon and enhances satiety.
  - It induces weight loss and decreases insulin dose.
  - Examples: PRAMLINTIDE
- Short-release bromocriptine
  - Effects: stimulates morning dopaminergic activity in brain and increases insulin sensitivity and decreases gluconeogenesis.
  - Side effects: GI symptoms, depression

Insulins and insulin analogues:

- These are administered as subcutaneous injections in abdomen, buttocks, arms and legs. These can also be administered as continuous subcutaneous insulin infusion (CSII).
- Usual starting dose is 0.5 – 1 units/ kg/ day.
- Regular insulin can be given intravenously in case of DKA.
- Insulins can be given as pre-mixed combinations: e.g. 70/30, 75/25, 50/50
- Basal-bolus regime:
  - Long acting insulin is given as basal insulin to cover baseline blood glucose levels.
  - Rapid acting insulin is given before meals to cover post-prandial spikes.
  - Some patients may just need a basal insulin without pre-prandial insulin. Some patients also may benefit from a basal insulin + METFORMIN combination.
  - Usual starting dose is 0.1 – 0.2 units/ kg if HbA1c is <8 % and 0.2 – 0.3 units/ kg if HbA1c is >8 %.
- If patient is unable to carry out an intensive insulin program:
  - Inj INSULIN 70/30 before breakfast and before dinner.
  - Give 2/3 of calculated dose in morning and 1/3 of calculated dose in evening.
  - Doses are adjusted according to fasting and 4:00 PM glucose.
- A sliding scale is sometimes used in inpatients.
  - Glucose is checkd pre-meals and at bed-time and regular insulin units are given accordingly. An intermediate-acting insulin is also given twice daily.
  - When patient is better, the total insulin units used per day can be used as the daily requirement of the patient on a pre-mixed combination.
- Modifications:
  - Patients undergoing surgery get 1/3 to ½ of the total dose and monitored.
  - Insulin should be decreased by 1 – 2 units for every 20 – 30 minutes of exercise.

Table 10.15: PHARMACOLOGY OF DIFFERENT INSULIN TYPES			
	Onset	**Peak**	**Duration**
RAPID ACTING (LISPRO, ASPART, GLULISINE)	15 minutes	30 – 90 minutes	3 – 5 hours
SHORT ACTING (REGULAR)	30 – 60 minutes	2 – 4 hours	5 – 8 hours
INTERMEDIATE ACTING (NPH aka ISOPHANE)	1 – 3 hours	8 hours	12 – 16 hours
LONG ACTING (GLARGINE, DETEMIR)	1 hour	Peakless	20 – 26 hours
ULTRA-LONG ACITNG (DEGLUDEC)	1 hour	Peakless	1 – 2 days

MONITORING TREATMENT:

- Monitoring of diabetes is done by both patient (self-monitoring of blood glucose) and physician.
- Targets of treatment are:
  - Fasting blood glucose: 80 – 130 mg/dL (ADA),<110 mg/dL (AACE)
  - 2-hour post-prandial glucose: 80 – 180 mg/dL (ADA) <140 mg/dL (AACE)
  - Pre-meals: 80 – 140 mg/dL (not routinely monitored),<110 mg/dL (AACE)
  - Glycated hemoglobin A1c (HbA1c): <6.5% for young active adults, <7% for average individuals, <8% for patients with renal or hepatic dysfunction, dementia and risk of hypoglycemia (ADA), <6.5% (AACE)
  - Absence of hypoglycemia

⇨ ***Most common cause of death in diabetes is coronary artery disease.***

10.4.2. DIABETIC KETOACIDOSIS (DKA)

"It is a condition of hyperglycemia, acidosis and ketonemia due to severe insulin deficiency."

QUICK FACTS: DIABETIC KETOACIDOSIS	
Pathology:	**Absolute deficiency of insulin → hyperglycemia, hyperketonemia, metabolic acidosis**
Presentation:	**Polydipsia, polyuria, nausea, vomiting, abdominal pain, muscle cramps**
Examination:	**Dehydration, Kussmaul's sign, fruity smell, features of hypovolemic shock, altered level of consciousness**
Diagnosis:	**ABGs, blood sugar, ketones, urea, creatinine, electrolytes, serum osmolarity**
Treatment:	**Intravenous fluids, insulin infusion, potassium replacement, manage underlying cause**

It is a medical emergency which is common in type 1 diabetes. It may also occur sometimes in type 2 diabetes in conditions of stress.
It is characterized by a triad of following:

- Hyperglycemia (blood glucose >250 mg/dL) – according to some >200 mg/dL
- Hyperketonemia (≥ 3.0 mmol/L) or ketonuria (>2+ on urine dipsticks)
- Metabolic acidosis (venous pH <7.30 and/ or bicarbonate <15.0 mmolL)

PATHOPHYSIOLOGY:

- Absolute deficiency of insulin → 1) loss of inhibiton of glycogenloysis and gluconeogenesis leads to hyperglycemia which causes osmotic diuresis and ultimately dehydration and electrolyte imbalances 2) loss of inhibition of hormone sensitive lipase leads to generation of free fatty acids which are utilized by liver for production of ketones (causes ketoacidosis) 3) acidosis and lack of insulin displaces potassium ions extracellularly which causes hyperkalemia as well as potassium losses 4) the condition is exacerbated by increased stress hormones e.g. catecholamines
- There are three important ketones namely: acetone, 3-beta-hydroxybutyrate, and acetoacetate.

PRECIPITATING FACTORS:

- Infections, discontinuation of or inadequate insulin, pancreatitis, myocardial infarction, stroke, certain drugs.

PRESENTATION:

- Usually presents with rapid onset of symptoms. It may be the initial presentation of type-1 diabetes.
- Symptoms:
  - Polydipsia, polyuria, weight loss, nausea, vomiting, weakness, blurred vision, abdominal pain, muscle cramps
- Signs:
  - Dehydration, poor skin turgor, Kussmaul's breathing, fruity smell (due to acetone), features of hypoperfusion due to volume loss (hypotension, tachycardia, cold peripheries, peripheral cyanosis), hypothermia, altered level of consciousness (confusion tocoma)

Table 10.16: CLASSIFICATION OF SEVERITY OF DIABETIC KETOACIDOSIS

	Mild DKA	Moderate DKA	Severe DKA
pH	7.25 – 7.3	7.0 – 7.24	<7.0
Serum bicarbonate	15 – 18 mEq/l	10 – 15 mEq/l	<10 mEq/l
Anion gap	>10	>12	>12
Mental status	Alert	Alert/ drowsy	Stupor/ coma

INVESTIGATIONS:

- Urea, creatinine: may indicate pre-renal to renal injury
- Electrolytes and blood gases: hyponatremia, hyperkalemia, high-anion gap acidosis
- Urinary and serum ketones: raised
- Serum osmolality: raised
- Other investigations to identify precipitating factors: ECG, complete blood count, blood culture, cultures from suspected site of infection, CRP, chest x-ray

MANAGEMENT:

- Principles of management include:
  - Adequate hydration
  - Insulin replacement
  - Potassium replacement
  - Management of other electrolytes
  - Management of precipitating factors
- Management:
  - Identify and manage the trigger.
  - Hydration:
    - Start with 0.9% saline and give 1 liter in one hour. Use 0.45% saline as initital fluid only if corrected sodium is >155 mmol/L.
    - Then continue 0.9% saline as 1 liter in next 2 hours →then 1 liter in next 2 hours → then 1 liter in next 4 hours →then 1 liter in next 4 hours →then as 1 liter in next 6 hours.
    - Use 0.45% saline if corrected sodium is ≥135 mEq/l and there is no hypotension.
    - Switch to 5% dextrose (or 10% dextrose) once glucose <250 mg/dL and then continue at around 125 ml/ hour.
    - Decrease fluid rates in elderly, pregnant, cardiac or renal failure.
  - Insulin:
    - Administer a STAT dose of regular insulin 0.1 units/ kg intravenously.
    - Make insulin infusion using 50 units REGULAR INSULIN in 50 ml of 0.9% saline.
    - Start infusion at 0.1 units/kg/hour.
    - Aim for glucose fall of ~ 55 – 110 mg/dL/hour. Rapid declines in glucose can lead to cerebral edema. Slower declines mean inadequate insulin replacement. If blood glucose is not falling according to target then increase infusion every hour till desired fall rate is achieved.
    - Once blood glucose is less than 200 mg/dL, decrease insulin infusion rate to 0.02 – 0.05 units/ hour and continue to resolution of DKA. Keep serum glucose in between 150 – 200 mg/dL.
  - Potassium:

        - Potassium replacement should begin with second fluid drip according to potassium level. It should be avoided or decreased if urine output <30ml/ hour.
        - If serum potassium in between 3.5 – 5.5 mEq/L then give 40 mmol of potassium in each liter of fluid. If level is <3.5 mEq/L then give additional potassium after expert advice. If level>5.5 mEq/L, then do not give potassium.
        - Stop replacement once insulin infusion is stopped.
        - Monitor cardiac rhythm in severe cases.
    - Acidosis:
        - No matter how severe the acidosis adequate fluid and insulin replacement improves acidosis.
        - Intravenous bicarbonate is not recommended because it causes cerebral edema and interferes with body's physiological responses.
    - Phosphate:
        - Patients are deficient in phosphate despite normal initial levels.
        - Replacement has not been found to be of much benefit and is currently not recommended unless there is severe hypophosphatemia, cardiac dysfunction or anemia.
    - Magnesium:
        - May be replaced as needed.
    - Monitoring:
        - Hourly monitoring of BP, pulse, oxygen saturation and urine output,
        - Hourly monitoring of glucose, ketones, venous bicarbonate and potassium.
        - Four-hourly monitoring of electrolytes.
        - Aims:
            - Fall in blood glucose 50 – 110 (60 – 80) mg/ dL/ hour.
            - Fall in blood ketones 0.5 mmol/ L/ hour
            - Rise in venous bicarbonate of 3 mmol/ L/ hour
        - Resolution is defined as blood glucose <200 mg/dL along with any two of following:
            - Bicarbonate ≥15 mEq/L
            - Venous pH >7.3
            - Calculated anion gap ≤12
        - Once resolution is achieved patient can be switched to subcutaneous insulin. Subcutaneous insulin should be given at least 1 – 2 hours before stopping insulin infusion.

COMPLICATIONS:

- Cerebral edema
- Acute respiratory distress syndrome
- Thromboembolism
- Disseminated intravascular coagulation
- Hypotension/ shock
- Hypoglycemia

Table 10.17: MANAGEMENT PRINCIPLES OF DIABETIC KETOACIDOSIS
Vigorous intravenous hydration
Insulin replacement
Correction of electrolyte imbalance
Identification and treatment of precipitating factor
Prevention of future episodes

10.4.3. HYPERGLYCEMIC HYPEROSMOLAR STATE (HHS)

"It is a condition of hyperglycemia without significant ketosis, due to relative insulin deficiency which leads to osmotic diuresis, increased serum osmolality and intravascular volume depletion."

QUICK FACTS: HYPEROSMOLAR HYPERGLYCEMIC STATE	
Pathology:	**Relative insulin deficiency → hyperglycemia → osmotic diuresis --> hyperosmolar state**
Presentation:	**Polydipsia, polyuria, altered level of consciousness, neurological deficits**
Examination:	**Dehydration, neurological examination**
Diagnosis:	**ABGs, blood sugar, ketones, urea, creatinine, electrolytes, serum osmolarity**
Treatment:	**Intravenous fluids, low dose insulin infusion, potassium replacement, manage underlying cause**

It is frequently seen in elderly type-2 diabetics and has high mortality rates (10-15%).Also called hyperosmolar non-ketotic coma.

PATHOPHYSIOLOGY:

- Relative insulin deficiency → hyperglycemia → osmotic diuresis → dehydration and depletion of intravascular water → decreased GFR → more hyperglycemia

PRECIPITATING FACTORS:

- Pneumonia, UTI with sepsis, myocardial infarction, cerebrovascular accident, inadequate free water intake, noncompliance with anti-diabetics, undiagnosed diabetes, renal failure, burns, medications (calcium channel blockers, chemotherapeutic agents, chlorpromazine, loop diuretics, olanzapine, phenytoin, propranolol, steroids), substance abuse (alcohol, cocaine).

PRESENTATION:

- Polydipsia, polyuria, altered level of consciousness, seizures, neurological deficits

Table 10.18: DIFFERENCES BETWEEN DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE

DIABETIC KETOACIDOSIS	HYPERGLYCEMIC HYPEROSMOLAR STATE
Usually presents with nausea, vomiting, abdominal pain and Kussmaul's breathing	Usually presents with polydipsia, polyuria and altered level of consciousness
Usually occurs in young type 1 diabetics	Usually occurs in elderly type 2 diabetics
Plasma glucose is usually more than 250 mg/dl	Plasma glucose is usually more than 600 mg/dl.
Effective serum osmolality is usually variable.	Effective serum osmolality is usually >320 mosm/kg.
Ketone bodies are raised	Ketonemia is absent Slight ketonuria may be present due to starvation
Acidemia is present	Acidemia is absent
Anion gap is increased mainly due to ketonemia	Anion gap is usually normal Small anion gap may be present due to lactic acidosis
Neurological status may or not be depressed.	Neurological status is always depressed.

INVESTIGATIONS:

- Blood sugar: typically more than 600 mg/dl (33.3 mmol/l)
- Serum osmolality: typically more than 320 mosm/kg

$$\boldsymbol{Effective\ serum\ osmolality\ in\ mosm\ per\ kg} = (\mathbf{2} \times \boldsymbol{sodium\ in\ meq\ per\ l}) + \frac{\boldsymbol{Glucose\ in\ mg\ per\ dl}}{\mathbf{18}}$$

- Ketone bodies in serum or urine may be slightly elevated due to starvation
- Electrolytes: Anion gap is usually normal (may be slightly raised due to lactic acidosis); serum potassium may be high; BUN and creatinine may be elevated due to dehydration
- Arterial blood gases: pH is usually >7.3
- Hematocrit: elevated due to dehydration

- ECG: always do to rule out MI
- Others: Other investigations may be related to underlying problems like sepsis.

MANAGEMENT:

- Identify and treat the trigger.
- Calculate corrected serum sodium

$$\textit{Corrected serum sodium} = \textit{Serum sodium in meq per l} + \frac{1.65 \times (\textit{Blood glucose in mg per dl} - 100)}{100}$$

- Hydrate patient (at least 9 l or 100 – 200 ml/kg in 48 hours).
- Start with isotonic fluids i.e. at least 1 – 3 l of normal saline over 2 – 3 hours.
- Calculate free water deficit and replace it over next 1 – 2 days first with half-normal saline and then with dextrose 5% water. Choice of fluids depends upon the corrected sodium level (half-normal saline for a corrected sodium ≥135 mEq/l and normal saline for corrected sodium <135 mEq/l).
- Initiate insulin therapy (IV bolus of 0.15 units/kg followed by maintenance rate of 0.1 units/ kg/ hour) and monitor blood sugars usually on an hourly basis. If the decline in blood sugars is inadequate (<75 – 100 mg/dl per hour), insulin infusion rate should be doubled.
- Replace potassium once urine output establishes as fluid and insulin therapy may lower potassium levels.

Table 10.19: CORRECTION OF POTASSIUM ACCORDING TO SERUM POTASSIUM

Serum potassium	Instructions	Potassium replacement	Aim
<3.3 mEq/l	Hold insulin	Replace potassium 2/3 as K-Cl 1/3 as K-phosphate	Bring potassium >3.3 mEq/l
3.3 – 5.0 mEq/l	-	20 – 30 mEq of potassium in each liter of fluid 2/3 as K-Cl 1/3 as K-phosphate	Maintain potassium in between 4.0 – 5.0 mEq/l
>5.0 mEq/l	-	Stop potassium replacement	Let potassium level decline to <5.0 mEq/l

- Replace phosphate if there is severe deficiency (<1 mg/dl) or if there is hypophosphatemia with respiratory depression, anemia or cardiac dysfunction.
- Replace magnesium deficiency, however rule out renal failure.
- Monitor electrolytes every one to two hourly in the beginning.
- Once plasma glucose falls below 250-300 mg/dl (13.9 – 16.7 mmol/l), add dextrose 5% water as IV fluid.
- Once patient starts taking food by mouth, switch to subcutaneous insulin and stop insulin infusion after half hour.
- Monitor the patient for thrombotic events like mesenteric artery occlusion, myocardial infarction, low-flow syndrome, and DIC and rhabdomyolysis.
- Monitor for complications like cerebral edema, osmotic demyelination, fluid overload, over-correction of electrolytes.
- Educate patient to avoid such instance in future.

10.4.4. DIABETES IN PREGNANCY

QUICK FACTS: DIABETES IN PREGNANCY	
Pathology:	**Placental hormones → insulin resistance** **Risk of maternal and fetal complications**
Presentation:	**Asymptomatic (should be screened)** **Maternal complications: increased risk of pre-eclamspsia and C-section** **Fetal complications: neural tube defects, macrosomia, birth injuries, microcephaly, congenital heart defects, hypoglycemia, respiratory distress**
Diagnosis:	**FBS, OGTT (FBS ≥92 mg/ dL. 1-hour post prandial ≥180 mg/dL. 2-hour post prandial ≥153 mg/dL)**
Treatment:	**Basal bolus insulin (best)** **Metformin, glyburide**
Targets:	**FBS <110 mg/dL. 2-hour post prandial <140 mg/dL. HbA1C <6.5%**

- Diabetes in pregnancy carries high risk to fetus and mother.

PATHOPHYSIOLOGY:

- Diabetogenic placental hormones → insulin resistance

COMPLICATIONS:

- Maternal complications: increased risk for pre-eclampsia and C-section
- Fetal complications: neural tube defects (e.g. anencephaly), microcephaly, congenital heart defects, caudal regression, birth injuries due to large-for-gestational age babies, shoulder dystocia, hypoglycemia, respiratory distress, neonatal encephalopathy, jaundice

PATIENTS AT RISK FOR GDM:

- BMI >30
- Previous macrosomic baby
- Previous GDM
- Family history of diabetes (first-degree relatives)
- Ethnicity

DIAGNOSTIC CRITERIA:

- Fasting blood sugar: ≥ 92 mg/dL
- 1-hour post-prandial: ≥ 180 mg/dL
- 2-hour post-prandial: ≥ 153 mg/dL

INVESTIGATIONS:

- Test for rubella, syphilis, hepatitis B virus, and HIV testing, as well as Pap smear, cervical cultures, blood typing
- May need testing for A1C, TSH, creatinine, urinary albumin-to-creatinine ratio

MANAGEMENT:

GDM:

- Smoking cessation counseling
- Review medications list for potentially teratogenic drugs e.g. ACEIs, ARBs, statins
- Refer for comprehensive eye exam. Dilated eye examinations should occur before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1-year postpartum as indicated by the degree of retinopathy and as recommended by the eye care provider.
- Renal assessment if not done before
- Continuous assessment of fetal growth and well-being
- Life-style changes: weight loss, diet and control on risk factors.
- Medical nutrition therapy (MNT).

- Pharmacological treatment:
    - Insulin (preferred agent)
    - Oral drugs that are useful: METFORMIN, GLYBURIDE
    - Basal-bolus regime is ideal with smaller basal dose (<50%) and larger bolus dose (>50%).
    - Prescribe low dose aspirin.
    - Prescribe prenatal vitamins (with at least 400 mg of folic acid)
- Glycemic targets:
    - Fasting blood sugar: <95 mg/ dL
    - 1-hour post prandial: <140 mg/ dL
    - 2-hour post prandial sugars: <120 mg/ dL

Pre-existing diabetes:

- Same as above
- BP targets may be relaxed as lower blood pressures may cause fetal growth retardation. ACEIs/ ARBs are contraindicated.
- Statins should be avoided.
- Advise elective birth by induction or C-section at 37 to 38 weeks.

POST-PARTUM CARE:

- Psychosocial assessment
- Self-care
- Encourage breast-feeding
- Test GDM for persistent diabetes or pre-diabetes at 4 – 12 weeks post-partum with a 75-g OGTT using non-pregnancy criteria (not A1C)

LONG-TERM CARE:

- There is increased life-time risk of developing diabetes in all GDM patients (50 – 70% at 15 – 25 years).
- Screen every 1 – 3 years.

10.4.5. HYPOGLYCEMIA

"It is a state of low blood glucose in blood which leads to deprivation of energy to tissues."

QUICK FACTS: HYPOGLYCEMIA	
Pathology:	**Low glucose → deprives cells of energy**
Presentation:	**Adrenergic symptoms: sweating, palpitations, tremors** **Neuroglycopenic symptoms: headache, diplopia, confusion, seizures**
Diagnosis:	**Clinical diagnosis, check blood sugar**
Treatment:	**Dextrose, glucagon**

- Clinical alert level is 70 mg/dL.
- Clinically significant hypoglycemia is classified at <54 mg/dL.
- Severe hypoglycemia: any level of hypoglycemia associated with severe cognitive impairment requiring assistance to recover.

PRESENTATION:

- Adrenergic symptoms: sweating, palpitations, hunger, tremors, hypertension, anxiety
- Neuroglycopenic symptoms: headache, diplopia, blurred vision, confusions, seizures, coma
- Whipple's triad:
    - Hypoglycemic symptoms are brought on by fasting.
    - Blood glucose <50 mg/dL during symptomatic attack.
    - Glucose administration improves symptoms.

INVESTIGATIONS:

- Usually no investigations needed if the trigger is obvious

- If unexplained hypoglycemia: plasma insulin, C-peptide, anti-insulin antibodies, plasma and urine sulfonylureas
- Workup of insulinoma if expected.

MANAGEMENT:
- If patient able to eat: give a rapid sugar product.
- If intravenous medicine necessary then 100 ml of dextrose 25% or 50 ml of 50% dextrose.
- Patients expected to have prolonged hypoglycemia are started on dextrose 5% or dextrose 10% infusions.
- All alcoholics or emaciated patients should get THIAMINE before getting glucose.
- Inj GLUCAGON in those patients at high risk of hypoglycemia.

Table 10.20: CAUSES OF HYPOGLYCEMIA
Drug-induced e.g. anti-diabetic drugs
Factitious
Insulinoma
Ethanol ingestion
Post-prandial after gastric surgery
Reactive/ idiopathic hypoglycemia
Addison's disease
Liver failure
Renal failure
Critical illness
Disorders of carbohydrate metabolism

10.4.6. INSULINOMA

"It is an insulin-producing tumor arising from beta-cells of the pancreas."

QUICK FACTS: INSULINOMA	
Pathology:	**Beta-cell tumor → increased insulin → hypoglycemia → adrenergic and neuroglycopenic symptoms**
Presentation:	**Adrenergic symptoms: sweating, palpitations, hunger, tremors Neuroglycopenic symptoms: headache, diplopia, blurred vision, confusion, seizures**
Diagnosis:	**72-hour fasting test, ultrasound, helical CT or MRI**
Treatment:	**Diazoxide + hydrochlorothiazide, octreotide, surgery**

CHARACTERISTICS:
- It is associated with MEN syndrome.
- It is benign in up to 90% of cases.

PATHOPHYSIOLOGY:
- Increased insulin secretion → hypoglycemia → adrenergic symptoms (due to sympathetic activation) and neuroglycopenic symptoms (due to hypoglycemia of nervous system)

PRESENTATION:
- Adrenergic symptoms: sweating, palpitations, hunger, tremors, hypertension, anxiety
- Neuroglycopenic symptoms: headache, diplopia, blurred vision, confusions, seizures, coma

INVESTIGATIONS:
- 72-hours fasting test:
  - Insulin levels are higher than expected for hypoglycemia (normally should be low).
  - C-peptide and proinsulin levels are also high (differentiate from exogenous insulin administration).
  - Sulfonylurea screen is negative (ruling out sulfonylurea abuse).
- Ultrasound

- Helical CT scan or MRI

MANAGEMENT:

- Symptomatic treatment:
  - DIAZOXIDE + HYDROCHLOROTHIAZIDE
  - OCTREOTIDE
- Surgical resection

⇨ ***Whipple's triad of insulinoma:***

1. ***Fasting brings about symptoms of hypoglycemia.***
2. ***Documented hypoglycemia at the time of symptoms (sugar <50 mg/dL).***
3. ***Glucose administration abolishes symptoms.***

⇨ ***Fourth criteria sometimes used: high insulin during hypoglycemia episode.***

10.4.7. GLUCAGONOMA

"It is a glucagon-producing tumor arising from alpha-cells of the pancreas."

PATHOPHYSIOLOGY:

- Alpha-cell tumors → secrete glucagon or have mass effects
- Glucagon → glycogenolysis, lipolysis, catecholamine secretion, inhibition of gastric and pancreatic secretions, excretion of water and electrolytes

PRESENTATION:

- Hyperglycemia and diabetes
- Necrotizing migratory erythema: pruritic maculopapular lesions and blisters → pustules → hyperpigmentation
- Others: glossitis, stomatitis, weight loss, diarrhea

INVESTIGATIONS:

- High glucose and glucagon levels; low amino acid levels

MANAGEMENT:

- Surgical resection

10.4.8. ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

"It is a gastrin-secreting tumor."

QUICK FACTS: ZOLLINGER-ELLISON SYNDROME	
Pathology:	**Tumors with increased gastrin → increased acid secretion and ulceration, diarrhea**
Presentation:	**Recurrent peptic ulcers, usually refractory to treatment, ulcers at unusual sites, diarrhea, malabsorption**
Diagnosis:	**Fasting gastrin level** **Secretin stimulation test** **Basal acid output** **Somatostatin receptor scintigraphy**
Treatment:	**High does PPI, resection, debulking surgery, chemotherapy**

FEATURES:

- 40% (benign), 60% (malignant)
- 80% (sporadic), 20% (associated with MEN-1)

LOCATION:

- 90% are located in gastrinoma triangle and arise from duodenum, pancreas or abdominal lymph nodes.
- 10% are located outside these locations: heart, ovary, gall bladder, liver, kidney, etc.

PATHOPHYSIOLOGY:

- Increased gastrin → increased acid secretion → mucosal ulceration → pain, diarrhea and malabsorption
- Increased gastrin → mucosal hypertrophy → increased number of parietal cells → increased acid secretion → mucosal ulceration → pain, diarrhea and malabsorption

PRESENTATION:

- Patients develop recurrent peptic ulcerations, ulcers refractory to treatment, ulcers at unusual sites, diarrhea or malabsorption.
- Typical symptoms include abdominal pain, diarrhea, heartburn, nausea, vomiting, weight loss and GI bleed.
- Associations: MEN-1
- Complications: perforation, esophageal stricture, GI bleed

INVESTIGATIONS:

- Fasting gastrin level: raised
- Secretin stimulation test: secretin fails to inhibit gastrin
- Basal acid output (BAO) >15meq/hour
- Serum calcium: raised (especially in MEN-1)
- Somatostatin receptor scintigraphy

MANAGEMENT:

- High-dose proton pump inhibitors
- Surgical resection
- Debulking surgery and chemotherapy

10.4.9. SOMATOSTATINOMA

"It is a somatostatin-producing tumor arising from D-cells of the pancreas."

- They are usually malignant.

PATHOPHYSIOLOGY:

- Somatostatin inhibits secretion of insulin, glucagon, growth hormone, gastrin, cholecystokinin, secretin and VIP.

PRESENTATION:

- Diabetes, cholelithiasis, weight loss, steatorrhea and hypochlorhydria.

ASSOCIATIONS:

- Neurofibromatosis

INVESTIGAITONS:

- Fasting serum somatostatin, transhepatic portal venous somatostatin, Ct scan, MRI, somatostatin receptor scintigraphy

MANAGEMENT:

- Surgery, chemotherapy

10.4.10. VIPOMA (VERNER-MORRISON SYNDROME)

"It is a VIP-producing neuro-endocrine tumor."

- They are usually malignant.

PATHOPHYSIOLOGY:

- VIP → stimulates cAMP production → increases intestinal secretions

PRESENTATION:

- Profuse secretory diarrhea, dehydration, electrolyte disturbances, weight loss

ASSOCIATIONS:

- MEN 1

INVESTIGATIONS:

- Renal function tests, electrolytes, VIP levels, CT scan, MRI, somatostatin receptor scintigraphy

MANAGEMENT:

- Correct electrolyte abnormalities
- Somatostatin analogues
- Glucocorticoids
- Chemotherapy
- Surgeical resection

10.5. DISEASES OF ADRENAL GLANDS

10.5.1. CUSHING'S SYNDROME

"It is a syndrome of excessive secretion of cortisol."

QUICK FACTS: CUSHING'S SYNDROME	
Pathology:	**Excessive secretion of cortisol → widespread metabolic and anti-inflammatory effects**
Presentation:	**Central obesity, moon face, buffalo hump, abdominal purplish striae, thin limbs, plethora, hirsutism** **Hypertension, proximal myopathy** **Insulin resistance or diabetes, osteoporosis**
Diagnosis:	**Screening: low-dose dexamethasone suppression test, 24-hour urinary cortisol** **High-dose dexamethasone suppression test, ACTH, CRH stimulation test**
Treatment:	**Iatrogenic: stop steroids** **Primary: surgery, drugs e.g. mitotane, ketoconazole, metyrapone, etomidate** **Secondary: trans-sphenoidal surgery, pasireotide** **Ectopic: surgery**

- Cushing's disease is caused by excessive secretion of ACTH from pituitary adenoma.

CAUSES:

- Iatrogenic (MOST COMMON)
- Adrenal causes: adenoma, carcinoma
- Cushing's disease/ ACTH-secreting pituitary adenoma
- Ectopic ACTH secretion: small cell carcinoma of lung, bronchial carcinoid, thymoma

PATHOPHYSIOLOGY:

- Increased cortisol → 1) widespread effects on carbohydrate, fat and protein metabolism lead to gluconeogenesis, lipolysis, fat redistribution, protein catabolism 2) anti-inflammatory effects 3) weakens immune response, etc.

PRESENTATION:

- Changes in appearance: central obesity, moon facies, buffalo hump, thin limbs, fat pads above supraclavicular fossae
- Skin changes: purple striae on abdomen, thin skin, easy bruising, plethora, lanugo hair, acne
- Androgenic effects: hirsutism,
- Hypogonadism: menstrual irregularity, infertility
- Salt retention: hypertension
- Insulin resistance: pre-diabetes, diabetes

- Musculoskeletal changes: proximal myopathy (wasting and wasting), osteoporosis, aseptic necrosis of femoral head
- Psychiatric changes: depression, mania, euphoria
- Others: increased infections, poor wound healing

INVESTIGATIONS:

- Overnight low-dose dexamethasone suppression test (SCREENING TEST)
  - 1 mg DEXAMETHASONE is given to patient at 11 PM.
  - Serum levels are measured at 11 PM.
  - Levels <5 can exclude the diagnosis while >5 are likely to have Cushing's disease.
- 24-hour urinary free cortisol (SCREENING TEST)
- High-dose dexamethasone suppression test
  - >50% suppression indicates Cushing's disease
  - Suppression is absent in adrenal/ ectopic ACTH causes.
- ACTH levels:
  - Low levels suggest adrenal or iatrogenic cause whereas high levels suggest pituitary adenoma or causes with ectopic ACTH secretion.
- CRH stimulation test:
  - Increase in ACTH or cortisol indicates Cushing's disease
  - No increase in ACTH or cortisol indicates adrenal tumor
- Imaging tests: CT/ MRI scans

MANAGEMENT:

- Iatrogenic: taper steroids
- Primary:
  - Surgical resection (patients should receive stress dose of steroids during and after surgery)
  - Drugs if surgery contraindicated e.g. MITOTANE, KETOCONAZOLE, METYRAPONE, ETOMIDATE
- Cushing's disease:
  - Trans-sphenoidal surgery
  - Somatostatin analogue PASIREOTIDE
- Ectopic: surgical resection

10.5.2. HYPERALDOSTERONISM

"It is excessive secretion of aldosterone by adrenal glands independent of renin-angiotensin system regulation."

QUICK FACTS: HYPERALDOSTERONISM	
Pathology:	**Increased aldosterone → sodium retention, potassium and hydrogen excretion**
Presentation:	**Hypertension** **Features of hypokalemia**
Diagnosis:	**Hypokalemia, mild hypernatremia, metabolic alkalosis, hypomagnesemia** **Screening: aldosterone-renin ratio** **Serum aldosterone, 24-hour urinary aldosterone, saline infusion test** **Tests for determining type of aldosteronism**
Treatment:	**Correct potassium** **Mineralocorticoid receptor antagonists** **Calcium channel blockers** **Adrenalectomy**

PATHOPHYSIOLOGY:

- Increased aldosterone → sodium retention + potassium and hydrogen excretion → hypertension, salt and water retention, hypokalemia and metabolic alkalosis

CAUSES:

- Adrenal adenoma or aldosteronoma (MOST COMMON)
- Adrenal hyperplasia
- Adrenal carcinoma
- Ectopic secretion of aldosterone e.g. ovarian and renal malignancy
- Glucocorticoid remediable aldosteronism (GRA)

PRESENTATION:

- Hypertension
- Features of hypokalemia: asymptomatic, fatigue, weakness, polydipsia, nocturnal polyuria
- Usually no peripheral edema

INVESTIGATIONS:

- Electrolytes and acid-base: hypokalemia, metabolic alkalosis, mild hypernatremia, mild hypomagnesemia
- Screening tests: Plasma aldosterone to renin ratio: usually >20 – 25 ng/dL (>900 pmol/L) in case of primary aldosteronism in case of primary aldosteronism
- Confirmatory tests: serum aldosterone level, 24-hour urinary aldosterone, serum aldosterone after saline infusion test, urinary aldosterone after oral sodium loading test
- Determination of type of primary aldosteronism:
    - Adrenal venous sampling for aldosterone
    - Furosemide stimulation test
    - Renin-aldosterone stimulation test
    - Imaging e.g. CT scan/ MRI of adrenals, iodocholesterol scan (differentiates hyperplasia from adenoma), areteriography/ venography

MANAGEMENT:

- General measures: correct hypokalemia
- Specific measures:
    - Mineralocorticoid receptor antagonists e.g. spironolactone, eplerenone
    - Calcium channel blockers particularly NIFEDIPINE
    - Glucocorticoids for GRA
    - Adrenalectomy in cases of aldosteronoma, hyperplasia refractory to treatment, carcinoma, etc.

10.5.3. PHEOCHROMOCYTOMA

"Pheochromocytoma is a catecholamine-secreting neuroendocrine tumor of the chromaffin cells of adrenal medulla."

QUICK FACTS: PHEOCHROMOCYTOMA	
Pathology:	**Excess catecholamines → increased adrenergic activity**
Presentation:	**Headache, sweating, anxiety, palpitations, sense of doom, chest pain, tremors**
Examination:	**Diastolic hypertension, tachycardia, orthostatic hypotension**
Diagnosis:	**Serum metanephrines** **24-hour urinary VMA or catecholamines** **Clonidine suppression test** **MIBG scan**
Treatment:	**Control hypertension: full alpha blockade then beta blockade** **Definitive treatment: surgical resection** **Metastatic disease: MIBG scan**

- It is a rare cause of secondary hypertension (<0.3%).

ASSOCIATIONS:

- Neurofibromatosis type 1, MEN IIa and IIb, Von Hippel-Lindau disease

PRESENTATION:

- **Symptoms:** headache, sweating (usually drenching), palpitations, anxiety, sense of doom, chest pain, tremors, constipation, nausea. Symptoms may present in episodes.
- **Signs:** usually sustained diastolic hypertension but classically may be paroxysmal (45%); tachycardia; orthostatic hypotension (because of catecholamine induced vasoconstriction and thus decreased blood volume); hypertensive retinopathy; weight loss; pulmonary edema; cardiomyopathy.

INVESTIGATIONS:

- 24-hour urinary catecholamines, metanephrines and vanillyl mandelic acid: Increased (highly sensitive and specific)
- Plasma fractionated metanephrines: Increased (highly sensitive but less specific)
- Clonidine suppression test
- Imaging studies: CT scan or MRI to look for adrenal tumor.
- MIBG (^{123}I meta-Iodobenzylguanidine) scan: to look for extra-adrenal tumors.
- Hyperglycemia

Table 10.21: 10 PERCENT RULE FOR PHEOCHROMOCYTOMA
• 10% are extra-adrenal (aka paragangliomas) while 10% of those are extra-abdominal. • 10% are bilateral. • 10% are malignant. • 10% are multiple. • 10% occur in children. • 10% are associated with MEN syndromes. • 10% of the tumors recur. • 10% are not associated with hypertension. • 10% are discovered incidentally.

MANAGEMENT:

- Surgical resection of tumor is treatment of choice.
- Phenoxybenzamine is started 7 – 10 days before surgery.
- Liberal salt water intake.
- Once adequate alpha-blockade has been achieved, start a beta-blocker (usually after two days).
- Perioperative hypertensive surges are controlled with intravenous phentolamine.

- Check plasma metanephrines 2 weeks after surgery then yearly for 10 years (life-long in case of genetic cause).
- Metastatic disease is treated with MIBG scan.

⇨ ***It presents classically as spells of a tetrad of headache, sweating, palpitations and severe hypertension.***

⇨ ***It is also said to present with 5 P's: pressure, pain, palpitations, perspiration and pallor.***

⇨ ***Alpha-blockers must be given adequately before initiating beta-blockers to avoid precipitating a hypertensive crisis.***

10.5.4. ADDISON DISEASE

"It is deficiency of steroid hormones due to dysfunction or absence of adrenal glands."

QUICK FACTS: ADDISON DISEASE	
Pathology:	**Deficiency of aldosterone → low sodium, high potassium**
Presentation:	**Fatigue, weakness, anorexia, weight loss, abdominal pain,**
Examination:	**Orthostatic hypotension, skin hyperpigmentation**
Diagnosis:	**Serum cortisol low** **Cosyntropin stimulation test positive** **Hyponatremia, hyperkalemia, non-anion gap acidosis, neutropenia, eosinophilia, fasting hypoglycemia**
Treatment:	**Steroid replacement**

PATHOPHYSIOLOGY:

- Low aldosterone levels →loss of sodium, retention of potassium

CAUSES:

- Autoimmune (MOST COMMON) – either isolated or as part of polyglandular syndromes
- Infections e.g. tuberculosis, coccidioidomycosis, histoplasmosis, cytomegalovirus, syphilis
- Bilateral adrenal hemorrhage
- Congenital: familial glucocorticoid deficiency, congenital adrenal hyperplasia
- Drugs e.g. mitotane, abiraterone
- Others: adrenoleukodystrophy, lymphoma, metastatic carcinoma, scleroderma, amyloidosis, hemochromatosis

PRESENTATION:

- Symptoms:
  - Fatigue, progressive weakness, anorexia, weight loss, abdominal pain, nausea, vomiting, diarrhea, fever, pains (arthralgias, myalgias, chest pain, abdominal pain, back pain), psychiatric features (anxiety, irritability, depression), orthostatic light-headedness, salt-craving
  - Sub-fertility, intra-uterine growth retardation, fetal loss
  - Features of hypoglycemia
  - Cerebral edema: headache, gait disturbances, vomiting, intellectual dysfunction
- Signs:
  - Low BP with orthostatic hypotension, skin hyperpigmentation (especially over knuckles, elbows, knees, posterior neck, palmar creases, gums, vermillion border of lips, nipples and areolas, skin folds, new scars), lymphadenopathy
  - Associated features: vitiligo, polyglandular syndromes, celiac disease, type 1 diabetes, Hashimoto thyroiditis, hypoparathyroidism, mucocutaneous candidiasis, etc.

Acute adrenal crisis:

- It is an emergency caused by severe deficiency of cortisol.
- It occurs during stress, sudden withdrawal of steroids in addison disease, bilateral adrenalectomy or removal of tumor, bilateral adrenal injury, thyroxine replacement in a patient with combined hypothyroidism and Addison disease.
- There is nausea, vomiting, fever, dehydration, shock which is refractory to fluids and vasopressors.

INVESTIGATIONS:

- CBC: neutropenia, lymphocytosis, eosinophilia
- Electrolytes and other minerals: hyponatremia, hyperkalemia, hypercalcemia, non-gap acidosis
- Serum glucose: fasting hypoglycemia
- Serum cortisol at 8:00 AM: <3 µg/dL (83 nmol/L) is diagnostic especially with elevated ACTH level >200 pg/mL (44pmol/L)
- Cosyntropin stimulation test: positive (hydrocortisone has to be stopped at least 8 hours before test)
- Serum DHEA levels: usually <1000 ng/mL (350 nmol/L)
- TSH: elevated in concomitant hypothyroidism
- Plasma renin: if elevated indicates need for fludrocortisone
- Others: low epinephrine levels, positive serum anti-adrenal antibodies and antibodies to 21-hydroxylase antibodies

MANAGEMENT:

- General measures:
    - Patient should wear a medical alert bracelet.
    - Infections are treated on priority basis.
    - Dose of steroids is increased in conditions of stress.
- Specific measures:
    - Oral HYDROCORTISONE 15 – 30 mg daily in two to three divided doses OR
    - Oral HYDROCORTISONE modified release form once daily
    - Oral PREDNISONE or METHYLPREDNISONE 3 – 6 mg daily in divided doses
    - In stress conditions, intravenous HYDROCORTISONE 50 – 100 mg STAT then 50 mg every 6 hourly.
    - If there is postural hypotension, hyponatremia or hyperkalemia not corrected by glucocorticoids or if plasma renin activity is increased → oral FLUDROCORTISONE 0.05 – 0.3 mg daily. If fludrocortisone is not tolerated, then oral SODIUM CHLORIDE tablets.
    - DHEA 50 mg once daily in morning in some women
    - In case of acute adrenal crisis:
        - Draw blood tests e.g. cortisol, ACTH, blood cultures, etc.
        - HYDROCORTISONE 100 – 300 mg STAT followed by 50 – 100 mg every 6 hours.
        - Treat electrolyte abnormalities.
        - Treat infections and precipitating factors.
        - Switch to oral once better.

10.6. MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

"Multiple endocrine neoplasia syndromes are rare inherited disorders in which there is over-activity and neoplastic growth of multiple endocrine glands."

- These are caused by autosomal dominant genetic mutations and tend to be familial.
- These can appear at any age.

INVESTIGATIONS:

- Genetic testing, hormone levels, imaging

MANAGEMENT:

- Relevant pharmacological treatment, surgical removal

Table 10.22: CLASSIFICATION OF MULTIPLE ENDOCRINE NEOPLASIA (MEN)

TYPE OF MEN	GENE	FEATURES
MEN 1 Wermer's syndrome	MEN1 (MENIN) tumor suppressor Chromosome 11	Parathyroid hyperplasia (>90%) → hypercalcemia Pancreatic islet tumors (e.g. gatrinoma, insulinoma, glucagonoma) Pituitary adenoma Facial angiofibromas Lipomas, collagenomas, gingival papules
MEN 2A Sipple's syndrome	RET proto-oncogene Chromosome 10	Medullary carcinoma of thyroid (>90%) Pheochromocytoma Parathyroid hyperplasia → hypercalcemia Lichen amyloidosis Hirschprung's disease
MEN 2B or 3 Multiple mucosal neuroma syndrome	RET proto-oncogene Chromosome 10	Medullary carcinoma of thyroid (>90%) Marfanoid habitus (100%) Mucosal neuromas (100%) Pheochromocytoma GI ganglioneuromas
MEN 4 or MEN X	Cyclin dependent kinase inhibitor (CDNK1B) mutations	Parathyroid adenomas Pituitary adenomas Tumors of reproductive organs, adrenals and kidneys

10.7. POLYGLANDULAR SYNDROMES

Aka autoimmune polyendocrine syndromes

"Polyglandular syndromes are a group of endocrine disorders characterized by

Table 10.23: TYPES OF POLYGLANDULAR SYNDROMES

TYPE 1	At least 2 of following: Hypoparathyroidism, chronic candidiasis, autoimmune adrenal insufficiency
TYPE 2 **Schmidt syndrome**	Autoimmune adrenal insufficiency + Autoimmune thyroid disease and/or type 1 diabetes mellitus
TYPE 3	Autoimmune thyroid disease + other autoimmune diseases (except autoimmune adrenal insufficiency, hypoparathyroidism, chronic candidiasis)
TYPE 4	Two or more organ-specific autoimmune diseases (which do not fall into type 1,2 or 3)

10.8. DYSLIPIDEMIAS

"These are metabolic disorders characterized by abnormal circulating lipids."

These abnormalities include:

- Elevated low-density lipoprotein cholesterol (LDL-C)
- Elevated triglycerides (TG)
- Low high-density lipoprotein cholesterol (HDL-C)

These are risk factors for atherosclerosis and coronary artery disease.
Elevated HDL-C >60 mg/dl is a negative risk factor for coronary artery disease.
Screen following:

- Age >40 years (males) or >50 years (females)
- Post-menopausal status
- Diabetes
- Hypertension
- Smoking
- Obesity
- Family history of premature coronary artery disease
- Presence of xanthomas, xanthelasmas or arcus cornealis
- Atherosclerotic vascular disease
- Erectile dysfunction
- Presence of RA, SLE, psoriasis, HIV positive patients receiving HAART, CKI

STATIN-BENEFIT GROUPS:

- Individuals with clinical atherosclerotic cardiovascular disease
- Individuals with primary elevation of LDL-cholesterol ≥190 mg/dL
- Diabetic patients aged 40 – 75 years and LDL-cholesterol 70 – 189 mg/dL
- Individuals with 10-year ASCVD risk >7.5% and LDL levels 70 – 189 mg/dL

Table 10.24: CLASSIFICATION OF HYPERLIPIDEMIA

Types	Name of hyperlipidemia	Lipoproteins	Lipids	Treatment
Type I	**Familial chylomicronemia** Cause: lipoprotein lipase (Buerger-Gruetz syndrome) or apolipoprotein CII deficiency (familial apoCII deficiency) Plasma appearance: creamy Presentation: acute pancreatitis, lipemia retinalis, eruptive skin xanthomas, hepatosplenomegaly	↑ Chylomicrons ↓ LDL, HDL	↑ Triglycerides	Diet control
Type IIa	**Familial hypercholesterolemia** Decreased or no functional LDL receptor expression Plasma appearance: clear Presentation: atherosclerosis, rest same as type I	↑ IIa-LDL ↑ LDL Normal or ↓ VLDL	↑ Cholesterol	Bile acid sequestrants Statins Niacin
Type IIb	**Familial combined hyperlipidemia** Cause: Overproduction of VLDL by liver Plasma appearance: clear or turbid Presentation: atherosclerosis, xanthelasma, arcus senilis, tendon xanthomas	↑ IIb-LDL, VLDL	↑ Triglycerides, cholesterol	Fibrates Nicotinic acid PCSK9 inhibitors
Type III	**Familial dysbetalipoproteinemia** Cause: Abnormal apolipoprotein E Plasma appearance: clear, cloudy or milky Presentation: atherosclerosis, tubo-eruptive xanthomas, palmar xanthomas	↑ IDL, ß-VLDL	↑ Triglycerides, cholesterol	Fibrates Statins
Type IV	**Familial hypertriglyceridemia** Cause: Overproduction and/or impaired metabolism of VLDL Plasma appearance: clear, cloudy or milky Presentation: atherosclerosis, pancreatitis	↑ VLDL Normal or ↓ LDL Normal or ↓ HDL	↑ Triglycerides	Fibrates Niacin Statins
Type V	**Familial mixed hyperlipidemia** Cause: increased production or decreased excretion of VLDL and chylomicrons Plasma appearance: creamy Presentation: pancreatitis	↑ VLDL, chylomicrons ↓ LDL, HDL	↑ Triglycerides	Niacin Fibrates

$$\textbf{Total cholesterol} = \textbf{LDL cholesterol} + \textbf{HDL cholesterol} + \frac{\textbf{Triglycerides}}{\mathbf{5}}$$

11. NEUROLOGY

11.1. HEADACHE

Headache can be divided into two types on basis of etiology:

- Primary
  - The condition is due to headache itself.
  - E.g. tension headache, migraine, etc.
- Secondary:
  - Headache is due to some other disease/ condition.
  - E.g. NSAID-induced headache, temporal arteritis, etc.

APPROACH TO HEADACHE:

Duration:

- Acute
- Sub-acute
- Chronic

Continuity:

- Intermittent: e.g. migraine
- Continuous: e.g. tension headache

Red flags:

- Sudden onset intense headache (thunderclap headache) usually signifies sub-arachnoid headache or sinus thrombosis
- Progressive focal neurological symptoms, weight loss and fever indicate cancer or chronic meningitis
- Onset after 50 years is worrisome for temporal arteritis and cancers
- Persistent morning headache with nausea/ vomiting signifies raised ICP
- Headache associated with postural change signifies raised ICP
- New onst unexpected headache
- Recent use of combined oral contraceptives
- History of cancer or HIV

Associated features:

- Migraine is associated with nausea, vomiting, photophobia and phonophobia. Headache may be unilateral or bilateral usually of a throbbing character and is brought on by certain stimuli e.g. chocolate, sunlight, menses, etc. It may be preceded by an aura.
- Unilateral peri-orbital pain with unilateral lacrimation, nasal congestion and redness of eye is associated with cluster headache.
- Headache of raised ICP occurs in early morning. It is vague headache associated with vomiting and may be relieved by analgesics. It may be associated with neurological findings which usually progress.
- Tension-type headache comes on with passage of day and is described as a band-like tightening around forehead. Pain seldom improves with analgesics and is present for a long time.
- Trigeminal neuralgia is associated with a lancinating pain which radiates to the front of jaw and is brought on by cold air or chewing.
- Giant cell arteritis is characteristically associated with a unilateral temporal headache with temporal tenderness. It may be associated with transient or permanent loss of vision as well as features of PMR.
- In case of subarachnoid hemorrhage, patient complains of sudden severe thunder-clap headache. It can also be desrived as worst headache of life. Patients develop altered level of consciousness and meningism.

Table 11.1: CAUSES OF HEADACHE	
Primary headaches	**Secondary headache**
Migraine Tension-type headache Cluster headache Other trigeminal autonomic cephalgias	Post-traumatic Idiopathic intracranial hypertension Neoplasm Hydrocephalus Substance abuse or its withdrawal Cerebral infarction Intracranial hemorrhage Giant cell arteritis Carotid or vertebral artery dissection Cerebral venous sinus thrombosis Headache due to refractory errors Glaucoma Headache due to ear, nose, sinus or throat disorders Dental problems Cervical spine arthritis

11.2. FACIAL PAIN

Table 11.2: DIFFERENTIAL DIAGNOSIS OF FACIAL PAIN	
Localcauses	Diseases of teeth and supporting structures Maxillary, ethmoid and frontal sinusitis Diseases of eyes, facial skin, salivary glands and pharynx
Neuropathic causes	Post-herpetic neuralgia Trigeminal neuralgia Glossopharyngeal neuralgia
Vascular causes	Migraine Giant cell arteritis Post-stroke pain Malignant neoplasms
Psychogenic causes	Atypical facial pain Burning mouth syndrome
Referred pain	Angina Lesions in neck and chest

11.3. SEIZURES

"A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in brain."

QUICK FACTS: SEIZURES	
Pathology:	**Uninhibited neuronal activity**
Presentation:	**Seizure = excessive electrical activity in brain Epilepsy = tendency to have recurrent seizures Classified into focal, generalized and unknown-onset seizures**
Examination:	**Witnessed seizure; Post-ictal findings; Focal neurological findings in case of secondary causes; Features of epilepsy syndromes**
Diagnosis:	**Clinical diagnosis; EEG; CT or MRI brain**
Treatment: (according to type of seizure)	**Absence seizure – ethosuximide Focal seizure – carbamazepine Focal seizure with secondary generalization – carbamazepine Generalized tonic-clonic seizure – valproate Myoclonic seizure – valproate**

EPILEPSY:

It is defined as a tendency to have recurrent seizures defined by any of the following:

- Two or more unprovoked seizures occurring >24 hours apart
- Single unprovoked seizure with a high 10-year risk of recurrence (>60%)
- Diagnosis of an epilepsy syndrome

RESOLUTION OF EPILEPSY:

- Individuals with age-dependent epilepsy syndrome beyond the applicable age
- Seizure-free for last 10-years and off-antiepileptics for last 5 years

A PROVOKED SEIZURE (AKA REACTIVE/ SITUATION-RELATED/ ACUTE SYMPTOMATIC SEIZURES):

- It is a seizure with a clearly identifiable temporally associated cause.
- The acute CNS insult may be caused by metabolic, toxic, structural, infectious or inflammatory lesions.
- It occurs in a person without a known tendency of seizures and has no tendency to recur unless the etiologic condition recurs e.g. meningitis, hyponatremia, etc.
- Seizures within one week after brain trauma, infection or stroke are not considered epilepsy. Those occurring after one week have high risk of recurrence.

EPILEPSY SYNDROMES:

- These are inherited or acquired conditions having seizure tendency with particular features (e.g. typical age, presentation, etc.) and other systemic features.
- Examples: Angelman syndrome, childhood absence epilepsy, Doose syndrome, epilepsy with generalized tonic-clonic seizures alone, frontal lobe epilepsy, temporal lobe epilepsy, juvenile absence epilepsy, West's syndrome, Lennox-Gestaut syndrome, neurocutaneous syndromes (neurofibromatosis, Sturge Weber syndrome, tuberous sclerosis complex), reflex epilepsies.

Table 11.3: OLD CLASSIFICATION OF SEIZURES

Partial seizures		Generalized seizures	Unclassified epileptic seizures
Simple partial: (sensory, motor, sensory-motor, psychic, autonomic) May evolve to secondary to secondary generalized	Complex partial: (with or without aura, with or without automatisms) May evolve to secondary to secondary generalized	Absence (typical or atypical) Myoclonic Clonic Tonic Tonic-clonic Atonic	-

ILAE 2017 (INTERNATIONAL LEAGUE AGAINST EPILEPSY) CLASSIFICATION OF SEIZURES

FOCAL (can occur with awareness or impaired awareness)		GENERALIZED		UNKNOWN ONSET	UNCLASSIFIED
Motor onset	**Non-motor onset**	**Motor**	**Non-motor (absence)**	-	-
Automatisms Atonic Clonic Epileptic spasms Hyperkinetic Myoclonic Tonic	Autonomic Behavior arrest Cognitive Emotional Sensory	Tonic-clonic Clonic Tonic Myoclonic Myoclonic-tonic-clonic Myoclonic-atonic Atonic Epileptic spasms	Typical Atypical Myoclonic Eyelid myoclonia	**Motor** Tonic-clonic Epileptic spasms **Non-motor** Behavior arrest	-

Changes: Partial → focal, simple partial → focal aware, complex partial → focal with impaired awareness, psychic → cognitive, secondarily generalized tonic-clonic → focal to bilateral tonic-clonic

TYPES OF SEIZURES:

These are classified as:

- Focal seizures: include temporal, frontal, occipital and parietal lobe seizures
- Generalized seizures: include generalized tonic-clonic seizures, tonic seizures and atonic/ astatic seizures.

Both seizure types can be either sub-clinical or clinical (either subtle or dramatic).

PATHOPHYSIOLOGY:

- Excitatory post-synaptic potentials (EPSPs) increase seizure tendency. These are caused by sodium influx, calcium influx and paroxysmal depolarization.
- Inhibitory post-synaptic potentials (IPSPs) decrease seizure tendency. These are caused by potassium efflux, chloride influx, and low pH.

CAUSES:

- Metabolic causes: hypoglycemia, hyponatermia, water intoxication, hypocalceia, uremia, hyperthyroidism, hyperthermia
- Structural brain lesions: scar tissue after cerebral infarcts or hemorrhage (scar epilepsy), metastases, primary brain tumors, brain abscess
- Infective causes: meningitis, encephalitis, septic shock
- Drugs: non-compliance with anti-epileptic drugs, acute withdrawal from alcohol, benzodiazepines or barbiturates
- Poisoning: cocaine, theophylline, lithium, amphetamine, lidocaine, metal toxicity (mercure, lead, etc.), carbon monoxide poisoning
- Congenital conditions and unidentified causes
- Others: TIA, increased intra-cranial pressure due to any cause, ecclampsia, hypertensive encephalopathy

PRESENTATION:

- Focal seizures:
    - Previously called partial seizures.
    - Any of cortical areas may be affected e.g. temporal, parietal, etc.
    - Previously described term "aura" is now classified as a focal seizure e.g. experience of burning odor is a focal seizure of olfactory cortex.
    - Temporal lobe seizures:
        - Most common type.
        - Often start with an aura e.g. epigastric rising sensation, stereotyped sense of fear.
        - Seizures are not dramatic.
        - Patients may present with:
            - Oral automatisms e.g. lip-smacking, chewing
            - Manual automatisms e.g. picking at clothes repeatedly, patting
            - Subtle dystonic posturing of a limb
            - "Jamais vu" (sense of eeriness) and "déjà vu" (sense of familiarity) phenomena.
        - Patients are unresponsive during the episode.
        - Afterwards patients may complain of fatigue, confusion, difficulty speaking or comprehending.
    - Frontal lobe seizures:
        - These are typically dramatic with obvious motor manifestations.
        - These often wake the patient from sleep.
        - Patients may have loud vocalizations, rhythmic movements of contralateral limbs, forced head turning, bicycling or Jacksonian marches or asymmetric dystonic postures.
        - Patients often are aware and conscious during the event.
    - Occipital lobe seizures:
        - Patients complain of sudden visual changes and then seizure my spread to other lobes causing other manifestations.
        - Primary visual cortex seizures: sees poorly formed colors or lights.
        - Supplementary visual cortex: sees stereotyped complex figures and detailed scenary.
    - Parietal lobe seizures:
        - Patients usually have subjective tingling or numbness or pain of contralateral limb or body.
- Generalized seizures:
    - Generalized tonic-clonic seizures:
        - Aura phase: The seizure may sometimes start with a vague aura.
        - Tonic phase: Patients suddenly lose consciousness. There is a loud cry of forced air breathed through closed vocal cords. There is tonic contraction of limbs and loss of postural control. Patient falls down and may develop secondary injuries due to fall.

        - Clonic phase: Limbs and head now start having clonic movements. More secondary injuries may occur during this period. Patients may develop urinary or fecal incontinence or tongue biting. Seizure episode may last 30 seconds to 3 minutes.
        - Post-ictal phase: Patients do not remember the event and may have dizziness, confusion or altered level of consciousness after the episode.
    - Absence seizures:
        - These usually occur in young childen.
        - There is sudden behavioral arrest, staring and unresponsiveness.
        - Seizure lasts 10 – 20 seconds.
        - Patients may repeated blinking or head nodding during the event.
        - Patients suddenly return to normal without post-event confusion.
        - Seizure may be elicited at the bed-side by asking the patient to hyperventilate.
    - Myoclonic seizures:
        - These are sudden fast and brief seizures which involve entire body or part of body.
        - Patients usually do not lose consciousness.
        - These may occur singly or repetitively.
        - These may have to be differentiated from physiologic myoclonus e.g. sleep startles.
    - Tonic seizures:
        - There is sudded loss of consciousness with adoption of a rigid posture.
        - These typically occur at night.
    - Atonic seizures:
        - There is sudden loss of consciousness and postural tone due to which patient falls to ground.
- Epilepsy syndromes:
    - These are different syndromes on the basis of history, clinical examination, seizure sub-type and EEG.
    - E.g. juvenile absence epilepsy, epilepsy with generalized tonic-clonic seizures, juvenile myoclonic epilepsy.

INVESTIGATIONS:

- Blood glucose, CBC, electrolytes, calcium
- Lumbar puncture if suggestive
- MRI brain: if focal symptoms r signs, focal seizures, or EEG findings of a focal cause.
- Electroencephalography (EEG)
    - Inter-ictal ECG may be normal.
    - Temporal lobe seizure: may show focal slowing or epiletiform discharges.
    - Frontal lobe seizure: may show para-sagittal focal slowing.
    - Generalized tonic-clonic seizure: spike-and-wave discharges (inter-ictal) or epileptiform (at start of event).
    - Absence seizure: regular generalized 3-Hz spike-and-wave pattern (during episode).
    - Myoclonic seizure: bursts of high-amplitude generalized spike or polyspike and wave activity.

MANAGEMENT:

- Goal of treatment: preventing further attacks
- Classify the type of seizure: focal, generalized or unknown. Classify the type of epilepsy: focal, generalized, combined focal and generalized or unknown. Classify into any epilepsy syndrome
- Consider etiology: structural, genetic, infectious, metabolic, immune or unknown
- Consider co-morbids of patient.
- Choose one drug according to type of epilepsy.
- Gradually increase the dose until seizures are controlled or side-effects become troublesome. If still seizures are not controlled then a seond drug is added. The second drug is gradually increased to target and the first is then gradually withdrawn.
- Drug levels may check on a seizure free dose for future reference.
- Surgical treatment is considered for patients unresponsive on two or more medicines. Vagal nerve stimulation is an alternative.
- Antiepileptic drugs are teratogenic but the risk of seizure in pregnancy far outweighs the side-effects. Newere generation anti-epileptics may be safer in this regards.

- Drugs are usually continued until the patient is seizure-free for at least two years.
- Other general rules:
    - Avoid in young females: valproate (teratogenic), phenytoin (gum hypertrophy, coarsening of facial features, hirsutism)
    - Consider hepatic enzyme induction: phenytoin, carbamazepine, barbiturates, oxcarbazepine, topiramate
    - Avoid in renal failure: gabapentin, levetiracetam, topiramate
    - Consider protein binding: phenytoin, valproate, tiagabine, carbamazepine, clonazepam, phenobarbital
    - Consider in pregnant females: lamotrigine, levetiracetam, gabapentin, clonazepam
    - Drugs which do not require monitoring: levetiracetam, lamotrigine, gabapentin
- Treatment of choices of different epilepsy types:
    - Absence seizures:
        - Acetazolamide, clonazepam, ethosuximide, lamotrigine, sodium valproate
    - Atonic seizures:
        - Phenobarbital, phenytoin, primidone, sodium valproate
    - Focal (partial) seizures:
        - Azetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, sodium valproate, tiagabine, topiramate, vigabatrin, zonisamide
    - Focal (partial) with secondary generalization:
        - Gabapentin, lacosamide, levetiracetam, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, sodium valproate, tiagabine, topiramate, vigabatrin, zonisamide
    - Focal seizures with secondary generalized tonic-clonic seizures:
        - Carbamazepine, eslicarbazepine acetate, lamotrigine, oxcarbazepine
    - Myoclonic seizures:
        - Clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, piracetam, sodium valproate
    - Tonic seizures:
        - Phenobarbital, phenytoin, primidone, sodium valproate
    - Tonic-clonic seizures:
        - Azetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, lamotrigine, Phenobarbital, phenytoin, primidone, sodium valproate, topiramate
- Individual ant-epileptic drugs:
    - Sodium channel blockers: stabilize sodium channels in the inactive state and prevent repetitive firing: PHENYTOIN, FOSPHENYTOIN, CARBAMAZEPINE, ESLICARBAZEPINE, LAMOTRIGINE, ZONISAMIDE, LACOSAMIDE
    - GABA receptor antagonists: CLOBAZAM, CLONAZEPAM, PHENOBARBITAL, PRIMIDONE
    - GABA reuptake inhibitors: TIAGABINE
    - GABA transaminase inhibitors: VIGABATRIN
    - Potential GABA mechanism: GABAPENTIN, PREGABALIN, VALPROATE
    - Glutamate blockers: FELBAMATE, TOPIRAMATE, PERAMPANEL
    - Neuronal potassium channel openers: EZOGABINE:
    - ACETAZOLAMIDE:
    - Others: LEVETIRACETAM, BRIVARACETAM, RUFINAMIDE, CANNABIDIOL, STIRIPENTOL

FIRST UNPROVOKED SEIZURE:

- In case of first seizure investigate to determine any provoking cause. Do EEG after 24 hours.
- The greatest risk of recurrence is within first two years.
- Increased risk of seizure recurrence:
    - Past stroke or head trauma
    - EEG with epileptiform abnormalities
    - Significant abnormality on brain-imaging
    - Nocturnal seizure

- Treatment of first unprovoked seizure with anti-epileptic drugs is not recommended as it does not improve the quality of life although it may reduce the short-term risk of seizures.
- Anti-epileptic drugs should be started if the patient with first unprovoked seizure has one or more ensuing seizures. These should also be initiated in patients with first unprovoked seizure and high risk of recurrence.
- Risk for adverse effects ranges from 7 – 31% and most are mild and manageable.

Table 11.4: ANTI-EPILEPTICS			
PHENYTOIN	Atonic seizures, focal seizures, focal seizures with secondary generalization, tonic seizures and status epilepticus. It is also class Ib anti-arrhythmic.	Status epilepticus: load with 10 – 15 mg/ kg iv at 25 – 50 mg/ min then continue 100 mg iv or oral 6 – 8 hourly. Seizures: 100 mg orally thrice daily which may be increased to 200 mg thrice daily.	Gingival hyperplasia, coarsening of facial features, nausea, vomiting, rash, blood dyscrasias, headache, vitamin K and folate deficiency, osteoporosis, ataxia, nystagmus, induces hepatic enzymes Teratogenic: cleft lip, cleft palate, congenital heart disease, mental retardation
FOSPHENYTOIN	Tonic-clonic seizures	Status epilepticus: 15 – 20 mg/ kg iv Seizures: load with 10 – 20 mg/ kg then give maintenance dose @ 4 – 6 mg/ kg/ day	Pruritis, dizziness, somnolence, ataxia, nystgmus, tinnitus
CARBAMAEPINE	Focal seizures, tonic-clonic seizures, focal seizures with secondary generalized tonic-clonic seizures, trigeminal neuralgia, bipolar mania.	200 mg orally 12 hourly and increase up to 1200 mg divided doses (increase every week by 200 mg)	Nausea, dizziness, diplopia, ataxia, elevated liver enzymes, induces cytochrome P450 system therefore interacts with multiple drugs. Idiosyncratic reactions: aplastic anemia, thrombocytopenia, agranulocytosis, Steven-Johnson syndrome.
ESLICARBAEPINE	Partial seizures	Dose: 400 – 1600 mg once daily	Dizziness, headache, somnolence, nausea
LAMOTRIGINE	Seizure disorder, partial seizures, bipolar disorder	50 mg once daily for two weeks then slowly increase every two weeks up to 300 – 500 mg/ day in tow divided doses	dizziness, diplopia, headache, ataxia, blurred vision, somnolence or insomnia, Steven-Johnson syndrome
LACOSAMIDE	Partial seizures	From 100 mg twice daily up to 150 – 200 mg twice dialy	Dizziness, diplopia, blurred vision, nausea, vomiting, fatigue, ataxia, nystagmus
CLONAZEPAM	Seizure disorder, panic disorder, essential tremors	1.5 – 20 mg/ day in three divided doses	Somnolence, abnormal co-ordination, ataxia, depression
PHENOBARBITAL	Status epilepticus, seizures, sedation	Status epilepticus: 15 - 18 mg/ kg iv loading dose Seizure: 1 – 3 mg/ kg/ day oral or iv in 1 – 2 divided doses	Respiratory depression, ataxia, dizziness, drowsiness
ACETAZOLAMIDE	Seizures, epilepsy, glaucoma	250 – 1000 mg daily in divided doses	Confusions, convulsions, drowsiness, flaccid paralysis
LEVETIRACETM	Myoclonus seizures, partial seizures,	500 – 1500 mg twice daily	Asthenia, headache, infection, increased blood pressure, somnolence, drowsiness

STATUS EPILEPTICUS:

QUICK FACTS: STATUS EPILEPTICUS	
Pathology and presentation:	**Single seizure lasting more than 5 minutes or two or more seizures within a five minute period without the patient becoming conscious** **Neurological emergency**
Diagnosis:	**Clinical + EEG** **Workup for precipitating cause**
Treatment:	**Thiamine, dextrose** **Give: lorazepam, midazolam or diazepam** **Also give: phenytoin, fosphenytoin** **If not controlled: phenobarbital, valproate** **If not controlled: intubate, ventilate and general anesthesia with midazolam, propofol or pentobarbital**

- It is defined as a single epileptic seizure lasting more than 5 minutes or two or more seizures within a five minute period without the patient becoming conscious.
- It is a medical emergency.
- The management includes:
- Maintain airway
- Give 25 – 50 ml of 50% dextrose or 100 ml or 25% dextrose and thiamine
- If seizures continue give:
    - LORAZEPAM 4m iv @ 2 mg/ min and repeat in 10 minutes if needed OR
    - MIDAZOLAM 10 mg IM and repeat in 10 minutes if needed OR
    - DIAZEPAM 0.2 mg/ kg as rectal gel
    - Watch for respiratory depression or hypotension.
- Give long-term seizure control with:
    - FOSPHENYTOIN 18 – 20 mg phenytoin equivalents iv at a rate up to 150 mg/ min OR
    - PHENYTOIN 18 – 20 mg/ kg at a rate of 50 mg/ min (do not give in dextrose solution)
- If seizures continue give:
    - PHENOBARBITAL 10 – 20 mg/ kg iv by slow or intermittent injection at 50 mg/ min OR
    - VALPROATE 20 –40 mg/ kg iv over 15 minutes
- If seizures still continue then general anesthesia with ventilatory support:
    - MIDAZOLAM 02 mg/ kg iv bolus then 0.05 – 2 mg/ kg/ hour OR
    - PROPOFOL 1 – 2 mg/ kg iv bolus followed by 2 – 15 mg/ kg hour OR
    - PENTOBARBITAL 15 mg/ kg iv bolus followed by 0.5 – 4 mg/ kg/ hour.
- Once seizures are controlled oral drugs ar started.

11.4. DYSAUTONOMIA

"It is an acute or chronic disorder of autonomic nervous system in which there is failure or over-activation of autonomic nervous system."

QUICK FACTS: DYSAUTONOMIA	
Pathology:	**Disturbed autonomic control**
Presentation:	**Cardiovascular: orthostatic hypotension, palpitations, exercise-induced syncope, fixed heart rate** **Urinary: frequency, urgency, incontinence** **Sexual: impotence, loss of libido, retrograde ejaculation** **Bowel: gastroparesis, intermittent diarrhea, nocturnal diarrhea, rectal incontinence** **Others: anhidrosis, hypothermia, burning feet, blurred or double vision**
Diagnosis:	**Orthostatic blood pressure and heart rate** **Ambulatory BP and EKG** **Tilt table test** **Cold pressor test** **Vesical ultrasound and urodynamic studies**
Treatment:	**Cardiovascular: good hydration, physical maneuvers, compression stockings, midodrine, fludrocortisone** **Urinary: anticholinergics, catheterization, vasopressin** **Sexual: sildenafil, tadalafil, prostheses** **Bowel: small meals, prokinetics**

The autonomic nervous system is concerned with control of following in different circumstances:

- Heart rate and blood pressure control and adjustement
- Control and co-ordination of different glands and gut
- Urinary control
- Pupillary control, focus and accommodation
- Lacrimation
- Control of sweating and shivering

Autonomic dysfunction can present with problems in control of any of the above.

TYPES:

- Primary:
  - Familial
  - Idiopathic orthostatic hypotension
  - Parkinson's syndrome
  - Multiple system atrophy
- Secondary:
  - Amyloidosis
  - Autonomic neuropathies e.g. GBS, myasthenia gravis, RA, diabetes, amyloidosis
  - CNS disease e.g. hypothalamic disease, syringomyelia, Wernicke's syndrome
  - Metabolic diseases e.g. Fabry's disease, pernicious anemia
  - Lambert-Eaton syndrome
  - Drugs e.g. alcohol, anti-depressants, anti-hypertensives, anti-psychotics

PRESENTATION:

- Cardiovascular:
  - Failure of compensatory mechanisms of blood pressure upon standing.
  - Patients present with orthostatic hypotension, light-headedness, fainting, dimness of vision, slurred speech, exercise-induced syncope andfixed heart rate.
- Urinary dysfunction: frequency, nocturia, urgency and stress incontinence.
- Sexual dysfunction: impotence, loss of libido, retrograde ejaculation or inability to achieve orgasm.
- Bowel dysfunction: intermittent diarrhea, nocturnal diarrhea, rectal incontinence, gastroparesis.
- Others: decreased sweating, hypothermia, burning feet, blurring or double vision

INVESTIGATIONS:

- Check bedside blood pressure and heart rate and recheck after standing for three minutes (increase in heart rate by 20/min or decrease in systolic blood pressure by 10 mmHg is diagnostic of orthostatic drop)
- Ambulatory blood pressure and EKG monitoring
- Tilt table test
- Cold pressor test
- Vesical ultrasound and urodynamic studies

MANAGEMENT:

- For orthostatic hypotension:
  - Hydration and increased salt intake
  - Avoidance of alcohol
  - Physical maneuvers upon symptoms e.g. sitting down, squatting, leg-raise
  - Compression stockings
  - Alpha-agonist: midodrine
  - Fludrocortisone
- Gastroparesis: small frequent meals, prokinetic drugs e.g. metoclopramide, cisapride, domperidone
- Post-prandial hypotension:octreotide
- Nocturia: avoid drinking water before bed-time, vasopressin
- Spastic bladder: anticholinergics (oxybutynin or tolterodine), intermittent catheterization
- Sexual dysfunction: sildenafil, tadalafil, prosthetic devices

11.5. STROKE

"It is rapid development of clinical signs of focal (at times global) disturbance of cerebral function, lasting for more than 24 hours or leading to death, with no apparent cause other than of vascular origin."

TYPES OF STROKE:

There are two main types of strokes:

- Ischemic stroke/ infarction: caused by vascular occlusion by thrombosis, embolism, etc.
  - Lacunar infarcts (15 – 30%):
    - These are small infarcts <5 mm in diameter.
    - They occur in regions supplied by short penetrating arterioles which originate from circle of Willis and supply basal ganglia, pons, cerebellum, internal capsule, thalamus and deep white matter.
    - They are caused by lipohyalinosis or microatheromatous narrowing due to poorly controlled hypertension or diabetes.
    - These may be asymptomatic or cause lacunar syndromes.
    - Partial or complete resolution may occur in 4 – 6 weeks.
  - Carotid circulation strokes:
    - These strokes occure in region of carotid circulation.
    - These are described in table.
  - Vertebrobasilar circulation strokes
    - They usually have symptoms of diplopia, vertigo, hearing loss, dysphagia, hiccups, circumoral numbness, decreased level of consciousness or bilateral symptoms. Examination may show dysconjugate gaze, Horner syndrome, nystagmus, unilateral pharyngeal weakness, ataxia and bilateral or crossed deficits.
    - These are described in table.
- Hemorrhagic stroke
  - They account for 20% of all strokes.
  - It is of two types:
    - Intraparenchymal hemorrhage – hemorrhage within brain parenchyma
    - Subarachnoid hemorrhage – hemorrhage within CSF-filled subarachnoid space

11.5.1. ISCHEMIC STROKE

QUICK FACTS: ISCHEMIC STROKE	
Pathology:	**Occlusion of blood supply to a particular region of brain → infarction → neurological deficit**
Presentation:	**Neurological deficits according to region involved**
Diagnosis:	**CT scan or MRI brain to rule out hemorrhage and know extent of infarct** **ECG, holter monitoring, echocardiography, carotid doppler ultrasound to look for cause** **Workup for risk factors**
Treatment:	**Stabilize patients** **Thrombolytics within 3 hours if no contraindications** **Mechanical embolectomy within 6 hours** **Secondary prevention: antiplatelets, anticoagulation if needed, control risk factors, carotid endarterectomy** **Manage complications** **Good nutrition, nursing care, physiotherapy, rehabilitation**

PATHOPHYSIOLOGY:

- Transient occlusion of blood supply → focal ischemia → temporary regional neurological loss
- Sufficiently occluded blood supply → infarction of nervous tissue, glia and vessels → regional neurological loss

RISK FACTORS:

- Diabetes, hypertension, smoking, dyslipidemia, advanced age, heart failure, coronary artery disease, atrial fibrillation, peripheral vascular disease, family history of stroke, previous history of stroke
- Oral contraceptive use, hypercoagulable states, hyperviscosity syndromes, sickle cell disease, cocaine or amphetamine abuse

STROKE CLASSIFICATION ON THE BASIS OF PROGRESSION:

- Evolving stroke/ progressing stroke/ stroke in evolution:
  - Strokes in which features worsen in first 24 – 48 hours.
  - It is usually due to gradual infarction within penumbra region.
- Completed stroke
  - Strokes in which there is maximum deficit at presentation and does not progress.
- Spectacular shrinking deficit:
  - Large hemispheric defect at presentation progressively improves to give rise to a smaller syndrome.
  - It is usually due to an embolus which lodges in a proximal vessel, but later breaks and migrates into smaller distal vessels.

CAUSES:

Main cause of stroke is atheroembolism leading to infarction. Rare causes can be low cardiac output, anoxia, hypoglycemia, anatomical abnormalities, hyper-coagulable and hyperviscous states and vasculitides.

- Embolism:
  - Heart: embolization of mural thrombi (atrial fibrillation, severe heart failure, cardiac aneurysm)
  - Internal carotid artery:
  - Aorta
  - Paradoxical: emboli from deep veins travel to right heart and pass through septal defects to left heart eventually reaching the brain.
- Thrombosis:
  - Carotid artery disease: atherosclerotic lesions in carotid arteries
  - Intra-cranial disease: atherosclerotic lesions in medium-sized arteries of brain.
- Small vessel disease:
  - Lumen narrowed due to thickening of vessels. The infarcts caused by their occusion are called lacunar infarcts.
- Non-vascular causes: hypotension, anoxia

PRESENTATION:

- Onset is sudden.
- Examination should focus on extent of deficit, localization of deficit and underlying causes.
- See table

INVESTIGATIONS:

- CT scan brain:
  - Perform immediately as soon as a stroke is suspected
  - It may not reveal infarction within first 6 – 12 hours but helps to rule out hemorrhage.
- MRI brain with diffusion-weighted images
  - Defines extent of infarct.
  - Essential before giving thrombolytics.
- Imaging of cervical vasculature using carotid duplex ultrasound, CTA or MRA
- Imaging of intracranial vessels using CTA or MRA
- CBC, PT, APTT, urea, creatinine, electrolytes, blood glucose, fasting lipid profile
- ECG or cardiac monitoring
- Echocardiography to look for cardiac causes
  - Echo with agitated saline will help in diagnosis of ASD or PFO.
- Cardiac enzymes in cases of suspected myocardial infarction
- Other specialized tests: tests for syphilis and HIV, screening for hypercoagulable states in young strokes or recurrent strokes, homocysteine levels, CSF examination, ESR, blood cultures

MANAGEMENT:

- Stabilizing patient:
  - Assess patients for circulation, airway and breathing
  - Intubate patients with very low GCS or unable to protect airway
  - Assess for aspiration
  - Admit in stroke care unit
  - Assess for swallowing and pass nasogastric tube if needed
  - Avoid passing foleys catheter and if passed then remove in 1 – 2 days.
  - Watch for signs of raised ICP, worsening neurological functions and herniation syndromes.
  - Keep head end elevated.
  - Give mannitol if signs of raised ICP.
  - Early decompressive craniotomy in case of malignant infarcts.
  - Do not lower blood pressure within 72 hours unless there is plan for thrombolysis, or neurological features are worsening or there is some indication to lower blood pressure e.g. active myocardial infarction, aortic dissection, or BP >220/110 mmHg.
- Minimizing disability:
  - Perform CT and CTA to rule out hemorrhage immediately (if patient presented within 6 hours of onset)
  - Consider thrombolytic therapy in patients presenting within 3 hours (can be given up to 4.5 hours) who do not have contraindications to thrombolysis (see table for contraindications)
    - Drug of choice is recombinant tissue plasminogen activator (rtPA)
    - Its dose is 0.9 mg/ kg up to a maximum dose of 90 mg. 10% of dose is given as bolus in one minute and the remaining dose is given in one hour.
    - Post-tPA care: Monitor patients closely for 24 hours. Do neurological exam and vital signs every 15 minutes for 2 hours, then every 30 minutes for 4 hours, then every hour for 18 hours. Maintain blood pressure <185/110 mmHg for at least 24 hours after tPA. Do not give anti-platelets or anti-coagulants for 24 hours. Avoid all invasive procedures for 24 hours. Repeat CT scan after 24 hours or immediately if neurological condition deteriorates.
    - Side-effects: hemorrhage (intra-cranial as well as elsewhere) – RISK OF DEATH IS NOT INCREASED
    - Patients who receive tPA within 3 hours are 30% more likely to have minimal or no disability at 3 months.
  - Consider endovascular mechanical embolectomy as adjunctive therapy in patients with large vessel occlusions within 6 hours of onset.
- Preventing recurrent strokes
  - Antiplatelets (reduce recurrence by 30%):
    - ASPIRIN 81 – 325 mg once daily or
    - CLOPIDOGREL 75 mg once daily or
    - ASPIRIN + DIPYRIDAMOLE 200 mg twice daily or
    - CILOSTAZOL 100 mg twice daily
  - Anticoagulants in case of atrial fibrillation, mechanical heart valves, etc.
  - Carotid endarterectomy
  - Control risk factors
- Manage complications:
  - Hemorrhagic transformation
  - Cerebral edema: elevate head-end, iv mannitol
  - Seizures
  - Aspiration pneumonia
  - Pressure-sores
  - Infections e.g. urinary tract infections, pneumonias
  - Depression
- Other elements of care:
  - Good nutrition

    - Preventing DVT with physiotherapy, compressive stockings or low-dose enoxaparin (40 mg subcutaneously daily)
- Rehabilitation
    - Physical therapy to prevent contractures and for early mobilization
    - Occupational therapy
    - Speech therapy
- PEG tube if there is need for long-term NG tube

Table 11.5: CONTRAINDICATIONS OF THROMBOLYSIS THERAPY

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
CT scan reveals hemorrhage Any history of intracranial hemorrhage, subarachnoid hemorrhage, intracranial aneurysm, AV malformation or tumor Significant head trauma or prior stroke in previous 3 months Recent intracranial or intraspinal surgery within last 3 months Severe uncontrolled hypertension i.e. SBP >185 mmHg or DBP >110 at the time of diagnosis (but blood pressure can be lowered immediately to <185/110 mmHg if thrombolysis is to be given). Thrombocytopenia (platelet count <100,000/ µL) or coagulopathy (PT > 15 seconds or INR >1.7 or APTT >1.5 times normal) Recent heparin therapy in last 48 hours unless APTT is <1.5 times normal Recent anticoagulation unless INR is <1.7 Recent therapeutic dose of low-molecular weight heparin in last 24 hours Blood glucose <50 mg/ dL or >400 mg/ dL Lumbar puncture within last 7 days	Seizure at onset Rapidly improving or minor symptoms Pregnancy Major surgery within last 14 days GI or urinary tract hemorrhage within last 21 days Myocardial infarction within last 3 months Dementia Arterial puncture of a non-compressible vessel Advanced age Severe stroke and coma (NIHSS score >25)

Table 11.6: STROKE SYNDROMES IN BRAIN-STEM

Region	Blood vessel	Features
Medulla	Anterior spinal branch of distal vertebral artery	**Medial medullary syndrome:** Contralateral hemiparesis (arm and leg) Ipsilateral weakness of tongue Contralateral sensory loss
	Distal vertebral artery or posterior inferior cerebellar artery	**Lateral medullary (Wallenburg) syndrome:** Ipsilateal limb ataxia Sensory loss on ipsilateral face and contralateral half of body Ipsilateral Horner syndrome Vertigo, nystagmus, nausea, vomiting, hiccups, hoarseness
Pons	Paramedian pontine branches from basilar artery	Contralateral hemiparesis (arm and leg) Contralateral ataxia Ipsilateral facial and abducens weakness with paralysis of conjugate gaze to the side of infarction (inferior infarcts) Contralateral facial weakness and inter-nuclera ophthalmoplegia (superior infarcts)
	Anterior inferior cerebellarartery	Ipsilateral limb ataxia Sensory loss on ipsilateral face and contralateral half of body Vertigo and nystagmus Unilateral deafness and tinnitus Ipsilateral facial weakness and Horner syndrome
	Superior cerebellar artery and long circumferential branches of basilar artery	Ipsilateal limb ataxia Dysarthria Contralateral hemianesthesia Ipsilateral Horner syndrome Ipsilateral choreoathetosis
Mid-brain	Paramedian peduncular branches of proximal PCA	**Weber syndrome:** Contralateral hemiparesis Ipsilateral paresis of medial rectus and vertical gaze with mydriasis
	Paramedian tegmental branches of PCA	Ipsilateral paresis of medial rectus and vertical gaze with mydriasis Contralateral limb ataxia Contralateral choreoathetosis and hemiballism

Table 11.7: FEATURES OF DIFFERENT STROKE SYNDROMES		
Stroke syndrome	**Blood vessel involved**	**Clinical features**
Anterior cerebral artery syndromes	MCA main stem	Contralateral hemiparesis (complete paralysis) Contralateral sensory loss (pain and temperature relatively intact) Homonymous hemianopia Contralateral conjugate gaze paresis (**looks towards the lesion**) Global aphasia (dominant) Impaired spatial perception and contralateral neglect (non-dominant)
	MCA superior division	Contralateral hemiparesis (face and arm > leg, distal > proximal) Contralateral sensory loss (face and arm > leg, distal > proximal) Contralateral conjugate gaze paresis No homonymous hemianopia Motor aphasia (dominant) Hemineglect and spatial disorders (non-dominant)
	MCA inferior division	Contralateral homonymous hemianopia or quadrantanopia Usually no weakness, sensory loss or gaze paresis Sensory aphasia (dominant) Contralateral neglect, problems with spatial perception, behavioral disorders (non-dominant)
Anterior cerebral artery syndromes	Unilateral ACA	Contralateral lower limb weakness (distal > proximal) Contralateral lower limb sensory loss (distal > proximal) Pseudo-paresis of contralateral arm due to neglect (supplementary motor area) Impaired initiation of speech Urinary incontinence
	Bilateral ACA	Bilateral lower limb weakness and sensory loss Behavioral abnormalities e.g. abulia, motor inertia, akinetic mutism Urinary incontinence
Ophthalmic or central retinal artery	Ophthalmic or central retinal artery	Sudden painless visual loss with pale retina and cherry-red spot on retina (TIA of this artery causes transient loss of vision aka amaurosis fugax)
Internal carotid artery syndromes	Internal carotid artery	Asymptomatic (if good collateral circulation) Infarction in region of anterior, middle and posterior cerebral artery (infarcts can occur in water-shed areas if blood supply is critically compromised)
Posterior cerebral artery syndromes	Posterior cerebral artery	Contralateral homonymous hemianopia (there may be macular sparing if there is collateral circulation from MCA) Alexia without agraphia (dominant)
	Bilateral PCA	Complete cortical blindness (there may be true tunnel vision if there is collateral supply from MCA) Anton syndrome (patient is unaware of blindness) May have impaired memory
	Proximal PCA occlusion	Thalamic infarction or mid-brain infarction (Weber syndrome)
Vertebrobasilar syndromes	Superior cerebellar artery	Dysarthria, ipsilateral limb ataxia, truncal ataxia, nystagmus
	Distal basilar artery	**Top of basilar syndrome:** Altered level of consciousness, Peduncular hallucinosis, Mid-sized unreactive pupils, Abnormal vertical gaze, Convergent nystagmus
	Proximal basilar artery	**Locked-in-syndrome: (bilateral ventral pons infarctions)** Quadriplegia with intact conscious level and intact vertical eye movements
	Other branches	See rest of brain-stem strokes
Lacunar syndromes	Branches supplying internal capsule, corona radiata or pons	Contralateral pure motor hemiparesis: contralateral weakness of face, arm and leg
	Branches supplying thalamus	Contralateral pure sensory stroke: contralateral sensory loss Dejerine-Roussy syndrome: severe pain and allodynia on affected side
	Branches supplying both internal capsule and thalamus	Sensorimotor stroke
	Branches supplying pons, internal capsule or corona radiata	Syndrome of ataxic hemiparesis: contralateral weakness and limb ataxia Dysarthria clumsy-hand syndrome: dysarthria and ataxia of upper limb

11.5.2. TRANSIENT ISCHEMIC ATTACK (TIA)

"It is a transient development of focal neurological symptoms and signs due to focal brain, spinal cord or retinal ischemia without infarction, in which all features resolve."

QUICK FACTS: TRANSIENT ISCHEMIC ATTACK	
Pathology:	**Ischemic of a particular region of brain → transient neurological deficit**
Presentation:	**Transient neurological deficit**
Diagnosis:	**CT scan or MRI brain to rule out hemorrhage and infarct** **ECG, holter monitoring, echocardiography, carotid doppler ultrasound to look for cause** **Workup for risk factors**
Treatment:	**Calculate ABCD2 score and hospitalize if needed** **Anti-platelets** **Anti-coagulation if needed** **Modify risk factors** **Statins**

- Most TIAs resolve within 1 hour (typical TIA).
- Previosuly TIAs were defined on the basis of duration (<24 hours) but up to 50% were actually found to be short-term strokes (infarction visualized on MRI).
- Reversible ischemic neurologic deficit (RIND):
    - Obsolete terminology.
    - Was used to define a stroke which lasted more than 24 hours but less than 3 days. Those lasting 1 – 7 days were called prolonged RIND.
- 30% of patients with stroke have history of TIAs.
- 5 – 10% of patients with TIAs develop stroke within next 3 months.
- Urgent intervention reduces rates of developing strokes.

CAUSES:

- Embolism:
    - Cardiac: atrial fibrillation, heart failure, infective endocarditis, non-bacterial thrombotic endocarditis, atrial myxoma, mural thrombi after myocardial infarctions
    - Paradoxical emboli: emboli originating DVT reach brain via atrial septal defect or patent foramen ovale.
    - Emboli originatin from ulcerated plaques in arteries supplying brain
- Atherosclerosis compromising intracranial or extranial arteries supplying blood to brain especially during hypotension
- Fibromuscular dysplasia
- Atherosclerosis of aortic arch
- Vasculitides e.g. giant cell arteritis, polyarteritis nodosa, granulomatous angiitis, tertiary syphilis
- Hematologic causes: hyperviscous and hypercoagulable states e.g. polycythemia, APLA syndrome
- Microthrombi in vessels e.g. sickle cell disease
- Subclavian steal syndrome: stenosis or occlusion of subclaian artery proximal to origin of vertebral artery shunts (steals) blood from vertebral artery to the arm

PRESENTATION:

- Transient neurological deficits of involved region
- Loss of consciousness is uncommon

INVESTIGATIONS:

- CT scan
- MRI brain with diffusion-weighted images to rule out small infarcts
- Carotid duplex ultrasonography
- CT or MR angiography
- Workup for risk factors and underlying causes
- ECG

- Echocardiography
- Holter monitoring or extended cardiac event monitoring

MANAGEMENT:

- Hospitalize all patients with ABCD2 score ≥4
- Prevent further attacks and development of stroke:
    - Assess for need of anticoagulation i.e. presence of atrial fibrillation, netallic heart valves, left ventricular thrombi, antiphospholipid antibody sydnrome
        - WARFARIN with target INR of 2.0 – 3.0 OR
        - RIVAROXABAN 20 mg daily OR
        - DABIGATRAN 150 mg twice daily OR
        - APIXABAN 2.5. – 5 mg twice daily
    - Start antiplatelets in case anticoagulation is not indicated.
        - ASPIRIN 81 mg once daily (preferred)
        - ASPIRIN + DIPYRIDAMOLE 200 mg twice daily
        - CLOPIDOGREL 75 mg once daily
        - CILOSTAZOL 100 mg twice daily
        - ASPIRIN + CLOPIDOGREL (good for short-term but has high risk of GI bleed on long-term basis)
    - Combined anticoagulation and antiplatelets: in patients with mechanical heart valves or in those with a coronary stenting
- Treat underlying risk factors
- Statins
- Surgical or endovascular measures if there is 70 – 99% stenosis in carotid arteries on the same of TIA
- General measures: stop smoking, weight loss

Table 11.8: ABCD2 SCORE FOR PREDICTION OF STROKE AFTER TIA

	CRITERIA	SCORE
A	Age ≥60 years	1
B	Blood pressure ≥140/ 90 mmHg	1
C	Clinical features • Unilateral weakness • Speech disturbance, no weakness	 2 1
D	Duration of symptoms • >60 minutes • 10 – 59 minutes	 2 1
D	Presence of diabetes	1
Interpretation: Score ≥4: start aspirin, specialist assessment within 24 hours Score <4: specialist referreal within one week Any score but TIA recurs in two weeks: high risk		
ABCD2I is better score with incorporation of I = infarcts on imaging having 3 points		

11.5.3. INTRAPARENCHYMAL HEMORRHAGE

"It is hemorrhage within the parenchyma of the brain."

QUICK FACTS: INTRAPARENCHYMAL HEMORRHAGE	
Pathology:	**Blood vessel rupture → hemorrhage within parenchyma**
Presentation:	**Neurological deficit, headache, vomiting, altered level of consciousness Features of raised ICP**
Diagnosis:	**CT or MRI brain**
Treatment:	**Stabilize patient Control BP (MAP 125 mmHg) Monitor ICP and treat with hypertonic saline or mannitol Surgical evacuation**

	VP shunt **Anti-epileptics** **Statins** **Secondary prevention: control BP**

- It accounts for 10 – 15% of all strokes.
- It is associated with high mortality.

PATHOPHYSIOLOGY:

- Rupture of blood vessel → hemorrhage within parenchyma → region supplied by vessel gets ischemia, blood exerts mass effect and also blood is metabolized into toxic intermediates → cerebral edema occurs around hematoma and causes neurological deteriorations
- Bleeding usually stops shortly or may continue for some time.

CAUSES:

- Hypertension
- Conversion of ischemic stroke into hemorrhage
- Amyloid angiopathy
- Anti-coagulation, anti-platelets or thrombolysis
- Brain tumors
- AV malformations
- Cerebrovenous occlusive disease

PRESENTATION:

- Sudden onset of neurological deficits, altered level of consciousness, headache and vomiting, signs of raised ICP

INVESTIGATIONS:

- CT scan brain immediately

Table 11.9: INTRACRANIAL HEMORRHAGE (ICH) SCORE FOR INTRAPARENCHYMAL HEMORRHAGE

PARAMETERS	VALUES	SCORES
GCS	3 - 4	2
	5 - 12	1
	13 - 15	0
ICH volume	≥30 ml	1
	<30 ml	0
Intra-ventricular hemorrhage	Yes	1
	No	0
Infratentorial origin	Yes	1
	No	0
Age ≥80 years	Yes	1
	No	0
Interpretation: (total scores with associated mortality) Score 0 = 0%, score 1 = 3%, score 2 = 26%, score 3 = 72%, score 4 = 97%, score 5 = 100%		

MANAGEMENT:

- Admit in intensive care.
- Maintain circulation, airway and breathing.
- Reduce blood pressure to a MAP of 125 mmHg (160/ 90 mmHg). Use labetalol or nicardipine.
- Intubation of patients who are unable to protect airway.
- Look for signs of trauma to head or cervical spine.
- Monitor ICP in selected patients.
- Treat raised ICP with hypertonic saline or mannitol.
- Steroids should be avoided as they are harmful.
- Surgical evacuation of selected bleeds e.g. cerebellar hematoma
- Ventricular drains in patients at risk of hydrocephalus.
- Prophylactic anti-epileptics in patients with lobar hemorrhage.
- DVT prophylaxis after 3 – 4 days if patient neurologically stable.

- Prevent recurrence:
    - Blood pressure control: thiazides or ACE inhibitors
    - Control risk factors

11.5.4. SUBARACHNOID HEMORRHAGE (SAH)

"It is hemorrhage into the CSF-filled subarachnoid space."

QUICK FACTS: SUBARACHNOID HEMORRHAGE	
Pathology:	**Bleeding into CSF space → 1) meningeal irritation 2) vasospasm of local blood vessels 3) blockage of CSF drainage leading to hydrocephalus**
Presentation:	**Sudden severe headache (thunder-clap headache), nausea, vomiting, altered level of consciousness**
Diagnosis:	**CT scan brain with CT angiography** **CSF for RBCs or xanthochromia** **Cerebral angiography**
Treatment:	**Nimodipine for vasospasm** **Surgical clipping or endovascular coiling of aneurysm** **VP shunt for hydrocephalus**

PATHOPHYSIOLOGY:

- Bleeding into CSF space → vasospasm of surrounding vessels causes infarction + blood irritates meninges + blood metabolites block arachnoid granulations and cause hydrocephalus

CAUSES:

- Trauma (MOST COMMON CAUSE)
- Ruptured berry aneurysms (MOST COMMON CAUSE OF SPONTANEOUS SAH)
- AV malformations

PRESENTATION:

- Severe headache:
    - Often described as the "worst headache of my life" or thunderclap headache
- Nausea, vomiting
- Altered level of consciousness
- Signs of meningism: photpphobia, phonophobia, neck rigidity
- Usually there are no preceding features of aneurysms
- Sub-hyaloid hemorrhage in retina on fundoscopy
- Complications:
    - Re-rupture
    - Vasospasm and infarction
    - Hydrocephalus
    - Seizures
    - SIADH
    - Death: first episode is fatal in about 25 – 50% of patients.

INVESTIGATIONS:

- CT scan brain with CT angiography:
    - May show finger-like or frond-like hyper-dense signals in sulci or hyperdense signals in cisterns
    - Patients may also develop infarctions or hydrocephalus
- If CT scan brain does not reveal SAH but there is still high suspicion then perform lumbar puncture and check CSF for red blood cells and xanthochromia
    - Lack of clearing of RBCs in last CSF bottle as compared to the first bottle indicates SAH and excludes traumatic tap. An absolute RBC count of $<2000 \times 10^6$/ L also does not favor SAH.

    - Xanthochrmoia is yellowish tinge in CSF due to degrading RBCs and is usually evident by 12 hours.
- ECG: may show cerebral T waves or arrhythmias
- Cerebral angiography once SAH is diagnosed

MANAGEMENT:

- Patients should be hospitalized and cared for. May need hospitalization for at least 14 days.
- Take neurosurgery consult.
- Definitive treatment:
    - Should be done ideally within 2 days
    - Options are surgical clipping of aneurysm or endovascular treatment by coil embolization
- Give calcium channel blockers to prevent vasospasm and infarctions
    - NIMODIPINE 60 mg orally every 4 hours for 21 days
- General measures:
    - Bed rest
    - Avoid any straining or exertion.
    - Give stool softeners or laxatives.
    - Analgesia for headache

11.6. STUPOR AND COMA

- Stupor is defined as a reduced state of alertness in which the patient is only responsive to painful stimuli.
- Coma is a reduced state of alertness in which the patient is minimally responsive or unresponsive to painful stimuli.
- Obtundation is a state in which a person has slowed responses to stimulation, less interest in surroundings and tends to sleep more than normal.

MANAGEMENT:

- Ensure airway, breathing and circulation.
- Check vitals: fever, respiratory rate, pulse rate, saturation, blood pressure
- Enquire about the symptoms which lead to the current situation e.g. symptoms of infection.
- Enquire about medical conditions e.g. diabetes, hypertension, endocrine diseases, epilepsy, etc.
- Enquire about drug history and any drugs found near patient.
- Enquire about trauma.
- General examination:
    - Look for anemia, jaundice, petechiae, rashes, signs of trauma, pressure ulcers, cellulitis, abscesses and lymphadenopathy.
- Neurological examination:
    - Check the level of consciousness using any good scoring scale e.g. Glassgow coma scale (GCS), or Alert Verbal Painful Unresponsive scale (AVPU).
    - Comment on speech if vocal.
    - Any focal/ localizing findings e.g. hemiparesis, unequal pupils, cranial nerve palsies, reflexes, etc.
    - Look for signs of meningeal irritation.
- Cardiovascular examination:
    - Examine for arrhythmias, murmurs, peripheral circulation and heart failure.
- Abdominal examination:
    - Examine for features of chronic liver disease.
    - Examine for abdominal sources of sepsis.
- Genitourinary examination:
    - Look for signs of genitourinary infection.
    - Monitor urine output.
- Investigations:
    - CBC, UCE, glucose, LFTs, ABG/ VBG, ammonia levels, TSH, cortisol, toxicology screen
    - CSF examination
    - Cultures
    - Chest x-ray, ultrasound abdomen

- CT brain
- In an unconscious patient with no known cause consider giving
  - Dextrose 25% 100 mL (also for known hypoglycemia)
  - Inj THIAMINE 100 mg iv or im (before or with dextrose)
  - Inj NALOXONE if suspected opioid poisoning
- Empiric antibiotics for suspected infections
- Antidotes of poisonings
- Correction of other underlying causes

Table 11.10: CAUSES OF ALTERED LEVEL OF CONSCIOUSNESS	
Traumatic	Diffuse axonal injury, concussion, contusion, epidural hematoma, subdural hematoma, subarachnoid hematoma, intraparenchymal hemorrhage, cerebral edema
Vascular	Infarction, intra-cerebral hemorrhage, subarachnoid hemorrhage
Neoplastic	Primary brain tumor, metastases
Infectious	Sepsis, bacterial meningitis, viral encephalitis, cerebral malaria, cerebral abscess
Metabolic	Hyponatremia, hypernatremia, hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, hypercalcemia, acidosis, alkalosis, myxedema coma, addisonian crisis, Wernicke's encephalopathy, uremia, hypoxia (due to any cause), hypercarbia (carbon dioxide narcosis due to any cause), hepatic encephalopathy
Drugs/ toxicities	Opioids, benzodiazepines, barbiturates Carbon monoxide poisoning, alcoholic intoxication, alcohol withdrawal syndrome, methanol ingestion, ethylene glycol ingestion, anticholinergic drug toxicity, serotonin syndrome, neuroleptic malignant syndrome, heavy metal poisoning
Miscellaneous	Hypertensive encephalopathy, seizure and post-ictal state, Status epilepticus, thrombotic thrombocytopenic purpura, hypothermia, heat-stroke, delirium due to any cause, advanced dementia, raised intracerebral pressure, hydrocephalus, basilar migraine, conversion disorder, myocardial infarction, ICU psychosis

11.7. INFECTIOUS AND INFLAMMATORY DISEASES

Table 11.11: INFECTIONS AFFECTING NERVOUS SYSTEM			
CATEGORIES OF INFECTIONS	**EXAMPLES**	**CATEGORIES OF INFECTIONS**	**EXAMPLES**
Viral infections	Viral meningitis Viral encephalitis Transverse myelitis Progressive multifocal leucoencephalopathy Subacute sclerosing panencephalitis Poliomyelitis Rabies HIV infection	**Fungal infections**	Cryptococcal meningitis Candida meningitis Brain abscess
		Protozoal infections	Toxoplasmosis Cerebral malaria Trypanosomiasis Amebic abscess Primary amebic meningoencephalitis
Bacterial infections	Acute bacterial meningitis Suppurative encephalitis Tuberculous meningitis Brain abscess Epidural abscess Neurosyphilis Polyneuropathy due to leprosy Polyneuropathy due to diphtheria Lyme disease Tetanus	**Helminthic infections**	Schistosomiasis Cysticercosis Hydatid disease Strongyloidiasis
		Prion-mediated infections	Creutzfeldt-Jakob disease Kuru Fatal familial insomnia

11.7.1. ACUTE BATERIAL MENINGITIS (ABM)

"It is an acute inflammation of the meninges and subarachnoid space caused by bacterial infection."

QUICK FACTS: ACUTE BACTERIAL MENINGITIS	
Pathology:	**Infection reaches meninges and subarachnoid spaces → inflammation**
Presentation:	**Acute presentation of fever, headache, neck stiffness, photophobia, phonophobia, nausea, vomiting, altered level of consciousness, seizures**
Examination:	**Signs of meningeal irritation: neck rigidity, Kernig's sign, Brudzinski's sign**

Diagnosis:	**Rule out raised ICP** **CSF analysis** **CT scan or MRI brain (contrast)**
Treatment:	**Steroids** **Empiric treatment: cephalosporin + vancomycin + acyclovir**

PATHOPHYSIOLOGY:

- CSF space is devoid of WBCs, immunoglobulins and complement

Bacteria reach meninges via:

- Hematogenous spread from nasopharynx (most common)
- Local spread from neighboring infected structures e.g. sinuses, middle ear, mastoid process
- Hematogenous spread from the body
- Directly via a congenital or acquired defect n skull or spine
- Directly after a neurosurgical procedure e.g. lumbar puncture, ventricular drain
- Directly via a penetrating wound

PRESENTATION:

- Symptoms: fever, headache, neck rigidity, altered mental status, nausea, vomiting, photophobia, phonophobia, seizures, rash
- General signs: fever
- Signs of meningeal irritation:
    - Nuchal rigidity: stiffness of neck on forward bending but not on side-to-side bending
    - Kernig's sign: First thigh is flexed at hip and knee is held at 90 degrees. Then knee is extended which causes pain and resistance to extension.
    - Brudzinski's neck sign: forced flexion of neck causes reflex flexion of hips.
    - Brudzinski's leg sign: passive flexion of knee onto abdomen leads to involuntarty flexion of opposite leg.
    - Jolt test: side-to-side movements of head lead to headache.
- Signs of raised ICP: papilledema, seizures
- Other specific features: purpuric rash (meningococcal meningitis), lung consolidation (S. pneumonia), heart murmurs (S. aureus or S. pneumonia)
- Complications: hydrocephalus, cranial nerve palsies (typically 6^{th}or 8^{th}nerve palsy), raised intra-cranial pressure, herniation, subdural empyema, septic shock, DIC, hyponatremia due to SIADH, stroke

INVESTIGATIONS:

- Lumbar puncture and CSF analysis: see table 11.12
- CSF for bacterial lipopolysaccharide antigens
- CSF PCR
- CT scan or MRI brain with contrast: meningeal enhancement, cerebral edema causing effacement of sulci

MANAGEMENT:

- Acute bacterial meningitis is a medical emergency. Antibiotics should be started immediately upon suspicion.
- Empiricial therapy should include:
    - DEXAMETHASONE 10 mg every 6 hourly for 4 days AND
    - A third or fourth generation cephalosporin (ceftriaxone 2 g iv twelve hourly, cefotaxime 2 – 3 g every 6 hourly, cefepime 2 g iv 8 hourly) AND
    - VANCOMYCIN 15 mg/ kg BD AND
    - ACYCLOVIR 10 mg/ kg 8 hourly
- Antibiotics may then be decreased according to cultures.
- Duration of antibiotics:
    - S. pneumonia: 10 – 14 days
    - H. influenza: 7 days
    - N. meningitidis: 3 – 7 days
    - L. monocytogenes:
- Penicillin G is the antibiotic of choice for suspected meningococcal meningitis.

- Give first shot of steroid at least half hour before antibiotics if possible.
- Perform lumbar puncture before starting antibiotics if possible.
- Treatment of raised ICP: elevation of head-end by 30 degrees, mannitol, intubation and hyperventilation.
- Managmement of complications
- Prophylaxis for close contacts of patients with meningococcal meningitis: RIFAMPICIN, CEFTRIAXONE, CIPROFLOXACIN

Table 11.12: COMMON CAUSATIVE ORGANISMS OF MENINGITIS ACCORDING TO AGE GROUPS

LIKELY ORGANISM IN ELDERLY	LIKELY ORGANISM IN ADULTS	LIKELY ORGANISM IN CHILDREN AND YOUNG ADULTS	LIKELY ORGANISM IN INFANTS
Streptococcus pneumonia (most common) Staphylococcus aureus Listeria monocytogenes Gram-negative bacteria	S. pneumonia (most common) S. aureus Neisseria meningitidis H. influenza	N. meningitidis S. pneumonia S. aureus Hemophilus influenza	Escherichia coli Group B streptococci L. monocytogenes
Preferred empiric drug	**Preferred empiric drug**	**Preferred empiric drug**	**Preferred empiric drug**
Ampicillin + ceftriaxone + gentamicin/ vancomycin Alternatively ampicillin + fluoroquinolone	Ceftriaxone + vancomycin Alternatively meropenem	Ceftriaxone + vancomycin if resistant Alternatively meropenem	Ampicillin + ceftriaxone Alternatively chloramphenicol + gentamicin

Table 11.13: CSF ANALYSIS IN DIFFERENT CONDITIONS

	Bacterial	Tuberculous	Viral	Fungal	Sub-arachnoid hemorrhage
Opening pressure	Elevated (usually >180 cmH2O)	Variable	Usually normal	Variable	Increased
Appearance	Turbid	Turbid or straw-colored	Clear	Clear	Grossly bloody, xanthochromic
White cell count	Increased (usually >1000 – 2000 cells/ µL)	Increased (usually 100 – 500 cells/ µL)	Increased (usually <2000 cells/ µL)	Increased (usually 100 – 500 cells/ µL)	May be increased due to bleeding (1 WBC for each 700 RBCs)
Differential cell count	Predominantly neutrophils	Predominantly lymphocytes or monocytes (neutrophils in initial stage)	Predominantly lymphocytes (neutrophils in initial stage)	Predominantly lymphocytes	Increased red cells (usually >2000/ µL)
Proteins	Elevated Usually >250 mg/dL	Elevated Usually 100 – 500 mg/ dL	Usually minimally elevated (<150 mg/ dL)	Normal to high	Increased (1 mg/ dL per 1000 RBCs)
Glucose	Low (usually 5 – 40 mg/ dL)	Low (usually <45 mg/ dL)	Normal (may be low in cases of HSV, CMV, mumps, lymphocytic choriomeningitis)	Low to normal	Normal
CSF glucose to serum glucose ratio	Usually 40%	Usually 40%	Usually >60%	Usually <60%	Usually >60%
CSF gram stain	60 – 90%	CSF AFB smear positive in 25%	Negative	Negative	Negative
CSF cultures	70 – 85%	CSF AFB cultures positive in 56%	50%	25 – 50%	Negative

⇨ ***Meninigits classically presents as a triad of fever, headache and neck rigidity.***

⇨ ***Streptococcus pneumonia is the most common causative organisms associated with meningitis.***

11.7.2. VIRAL MENINGITIS

- It comes under category of aseptic meningitis.

CAUSATIVE ORGANISMS:
- Coxsackievirus B, echovirus, HIV, HSV-2, West-Nile virus and others

PATHOPHYSIOLOGY:
- Viruses infect meninges and subarachnoid space

PRESENTATION:
- Fever, headache, neck rigidity, malaise, myalgia, nausea, vomiting, photophobia, diarrhea, rash

INVESTIGATIONS:
- CSF analysis (table 11.12), brain imaging

MANAGEMENT:
- Self-limited, acyclovir in HSV, anti-retroviral therapy in HIV

11.7.3. TUBERCULOUS MENINGITIS

"It is a chronic meningitis caused by mycobacterium tuberculosis."

QUICK FACTS: TUBERCULOUS MENINGITIS	
Pathology:	**Rich focus in brain ruptures in subarachnoid spaces → inflammation of meninges and purulent exudate aroud base of brain and cranial nerves**
Presentation:	**Subacute to chronic presentation of fever, headache, neck stiffness, altered level of consciousness, poor health, seizures**
Examination:	**Signs of meningeal irritation: neck rigidity, Kernig's sign, Brudzinski's sign Cranial nerve palsies**
Diagnosis:	**Rule out raised ICP CSF: chemistry, AFB smear and culture, PCR for MTB, ADA CT scan or MRI brain (contrast)**
Treatment:	**Anti-tuberculous therapy Steroids**

PATHOPHYSIOLOGY:
- Tuberculous bacilli reach meninges or brain parenchyma hematogenously → form tubercles (Rich foci)→ enlarges and ruptures into subarachnoid space → meningitis
- Inflammatory exudate around blood vessels → vasculitis → stroke
- Meningeal fibrosis → occludes arachnoid villi → communicating hydrocephalus

PRESENTATION:
- Usually sub-acute to chronic presentation
- Headache, anorexia, low-grade fever, poor health, neck stiffness
- Cranial nerve palsies e.g. 6^{th} nerve palsy
- Cognitive impairment (confusion progresses to coma)
- Increased ICP: nausea, vomiting, papilledema
- Focal signs due to stroke
- Features of TB elsewhere e.g. lungs, lymph nodes
- Complications: seizures, hydrocephalus, SIADH, syringomyelia, side-effects of ATT (neuropathy, optic neuritis, ototoxicity, hepatitis, etc.)

INVESTIGATIONS:
- CSF analysis: see table 11.12
- CSF adenosine deaminase: elevated

- CSF PCR test: high sensitivity and specificity
- CT scan or MRI brain with contrast: basal meningeal enhancement, thickened meninges
- Chest radiographs: findings of TB

MANAGEMENT:

- Anti-tuberculous therapy– Rifampin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z). All four drugs are given for first two months (intensive phase) while only isoniazid and rifampicin are given for next four to seven months (maintenance phase).
- Steroids are added along with ATT:
    - DEXAMETHASONE 0.15 mg/ kg oral or iv four times daily for one to two weeks then tapered over four weeks.

11.7.4. ACUTE VIRAL ENCEPHALITIS

"It is an inflammation of brain parenchyma caused by viruses."

QUICK FACTS: ACUTE VIRAL ENCEPHALITIS	
Pathology:	**Viral infection of meninges**
Presentation:	**Acute to subacute fever, headache, altered level of consciousness, personality changes**
Examination:	**Signs of meningeal irritation** **Focal neurological deficits**
Diagnosis:	**CSF analysis: chemistry, HSV PCR** **CT scan or MRI brain contrast**
Treatment:	**For HSV and VZV: Acyclovir** **For CMV: ganciclovir, foscarnet** **For most of others: conservative treatment**

Table 11.14: CAUSES OF VIRAL ENCEPHALITIS

Enteroviruses (including coxsackievirus, poliovirus and echovirus)	Measles
Herpes simplex virus (HSV) types 1 and 2	Rubella
Cytomegalovirus (CMV)	Rabies virus
Epstein-Barr virus (EBV)	Nipah
Varicella-zoster virus (VZV)	Eastern equine virus
Human herpes virus 6 (HHV-6)	West Nile encephalitis virus
Adenovirus	Colorado tick fever
Mumps	Japanese encephalitis virus

PRESENTATION:

- Acute to subacute onset
- Fever (usually low-grade), headache, altered level of consciousness (delirium or coma), personality changes, disturbances of perception, disorientation
- Signs of meningeal irritation
- Features of affected brain region e.g. aphasia, ataxia, movement disorders, visual field defects, seizures

INVESTIGATIONS:

- CSF analysis
    - HSV1 may have a hemorrhagic picture with xanthochromia or erythrocytic pleocytosis.
- MRIbrain with gadolinium contrast:
    - Shows increased signals in T2 weighted images
    - Hypoattenuation or hemorrhages in temporal or frontal areas in case of HSV

MANAGEMENT:

- Most viral encephalites are self-limiting and require supportive measures. Some may need anti-virals.

- HSV:
  - ACYCLOVIR 10 mg/ kg 8 hourly for 10 – 14 days
- VZV:
  - ACYCLOVIR
- CMV:
  - GANCICLOVIR, FOSCARNET

⇨ ***HSV is the viral encephalitis with the most dreaded complications: hemorrhagic necrosis of temporal or frontal lobes.***

11.7.5. INTRA-CRANIAL ABSCESS (BRAIN ABSCESS)

"It is an intra-cranial space occupying pus-filled lesion."

QUICK FACTS: INTRA-CRANIAL ABSCESS	
Pathology:	**Infectious organism reach brain parenchyma → local inflammation and suppuration**
Presentation:	**Headache, vomiting, altered level of consciousness, fever, seizures**
Examination:	**Focal neurological deficits** **Meningism**
Diagnosis:	**CT scan or MRI brain with contrast**
Treatment:	**Stereotactic needle or surgical aspiration and culture** **Antibiotics** **Mannitol, dexamethasone**

PATHOPHYSIOLOGY:

Spread of infectious organisms to brain parenchyma due to:

- Local spread from ear or nose infections
- Hematogenous spread from an infective focus anywhere in body especially in patients with congenital cyanotic heart disease, lung abscess, endocarditis, dental infection
- Direct introcduction due to trauma or surgery

Micro-organisms causing brain abscess:

- Streptococcus species (MOST COMMON)
- Staphylococci
- Bacteroides fragilis
- Others Enterobacteriaceae, Enterococci, Fusibacterium, Listeria monocytogenes, Hemophilus species, Toxoplasma gondii, Nocardia, Actinomyces, mycobacterium tuberculosis, fungi, etc.

PRESENTATION:

- Fever with chills
- Signs of raised intra-cranial pressure: headache, vomiting, altered level of consciousness (drowsiness, inattention, confusion), seizures
- Focal neurological deficits
- Herniation or intra-ventricular rupture of brain abscess:unconsciousness, signs of meningism

INVESTIGATIONS:

- CBC: neutrophilia
- CT scan or MRI brain with contrast: ring-enhancing lesion with surrounding edema
- Stereotactic needle aspiration: send for cultures, AFB and fungal cultures
- Lumbar puncture: usually contraindicated and also unyielding

MANAGEMENT:

- Start with empirical iv antibiotics:
  - CEFTRIAXONE 2 g iv twice daily +
  - METRONIDAZOLE 15 mg/ kg iv STAT then 7.5 mg/ kg iv every 6 hours +
  - VANCOMYCIN 1 g iv twice daily
- For cerebral edema:

- DEXAMETHASONE 4 – 25 mg four times daily iv or orally
- MANNITOL iv

- Switch to iv antibiotics according to culture and sensitivity results and continue for 6 – 8 weeks
- Monitor with imaging (CT or MRI) every 2 weeks or of patient deteriorates
- Some infections may need prolonged oral drugs e.g. nocardiosis, fungal infections and tuberculosis.
- Surgical drainage for large abscesses

11.8. DEMENTIAS

"These are progressive acquired deteriorations in cognitive functions without impairment of consciousness that interfere with activities of daily living."

Mild Cognitive Impairment (MCI): is defined as cognitive decline that does not affect activities of daily living.

Table 11.15: DSM-IV DIAGNOSTIC CRITERIA FOR DEMENTIA

Presence of following cognitive deficits which interfere with daily function and do not occur exclusively during delirium:

1. Memory impairment
2. At least one of the following: a) Aphasia b) Apraxia c) Agnosia d) Poor executive functioning

Table 11.16: CAUSES OF DEMENTIA

REVERSIBLE CAUSES	IRREVERSIBLE CAUSES
Metabolic disorders e.g. vitamin B12 deficiency, folate deficiency, thiamine deficiency	Alzheimer's disease (MOST COMMON)
Endocrine disorders e.g. hypothyroidism or hyperthyroidism, hypoparathyroidism	Parkinson
Medications e.g. anticholinergics	Vascular dementia
Toxic agents e.g. lead, alcohol	Dementia with Lew bodies
Infections e.g. neurosyphilis, TB meningitis, HIV	Huntigton's chorea
Normal pressure hydrocephalus	Unresetable mass lesion
Depression, schizophrenia	HIV dementia
Delirium	Korsakoff's syndrome
Subdural hematoma	Progresssive multi-focal leucoencephalopathy
Resectable tumors	Creutzfelddt-Jakob disease
	Wilson's disease
	Multiple sclerosis

Table 11.17: CAUSES OF DEMENTIA

CORTICAL DEMENTIA	SUBCORTICAL DEMENTIA	MIXED DEMENTIA
Mainly affect memory, language, perceptual functions and praxis There are no extra-pyramidal features.	Mainly affect behavior, affect, mood, motor processing, executive function. There are usually extra-pyramidal features.	Combined cortical and subcortical features
Examples: Alzheimer's disease Diffuse Lewy body disease Vascular dementia Frontotemporal dementia	Examples: Parkinson disease Progressive supranuclear palsy Normal pressure hydrocephalus Huntingtons disease Chronic meningitis	Examples: Vascular dementia Diffuse Lewy body disease Neurosyphilis

APPROACH:

- Thorough history
- Systemic examination
- Cognitive and neuropsychiatric examination e.g. Folstein's Mini-Mental State Examination (MMSE)
- Relevant investigations to rule out different causes
- Pharmacotherapy, nursing care and physiotherapy

11.8.1. ALZHEIMER'S DISEASE

"It is a neurodegenerative disorder causing dementia and is characterized by deposition of beta-amyloid plaques in hippocampus and other parts of brain."

QUICK FACTS: ALZHEIMER'S DISEASE	
Pathology:	**Accumulation of extra-cellular ß-amyloid plaques and intra-cellular tau-protein neurofibrillary tangles in various brain areas → atrophy → cognitive deficits**
Presentation:	**Progressive loss of cognitive dysfunction in elderly** **Early features: forgetfulness, poor concentration** **Intermediate features: short-term memory loss** **Late features: long-term memory loss, dependence**
Diagnosis:	**Clinical diagnosis** **Imaging**
Treatment:	**Anti-cholinesterases e.g. donepezil, rivastigmine, galantamine** **NMDA antagonists e.g. memantine** **Vitamin E**

PATHOPHYSIOLOGY:

- Extracellular senile plaques (ß-amyloid) and intracellular neurofibrillary tangles (tau proteins) accumulate in hippocampus, entorhinal area and other areas of brain →atrophy of affected structures → progressively increasing cognitive decline (memory → language → visuospatial).
- Aside from these, oxidative stress, inflammatory reactions and insulin resistane play role.

PRESENTATION:

- It usually occurs in >60 years of age and is characterized by progressive loss of cognitive functions. It appears early in familial forms and in Down syndrome. Death occurs in 5 – 10 years and is usually due to infections.
- Early features: mild forgefullness, poor concentration, personality changes, impaired judgement
- Intermediate features: memory loss (initially short-term but later long-term as well), denial of condition, apraxia, visuo-spatial impairment, depression.
- Late features: progressive dependence others for activities of daily living, paranoid delusions, hallucinations, aphasia, sphincter incontinence.

INVESTIGATIONS:

- It is a clinical diagnosis. Exclude other causes of dementia.
- Imaging studies: diffuse cortical atrophy with dilatation of ventricles

MANAGEMENT:

- Anti-cholinesterases: DONEPEZIL, RIVASTIGMINE, GALANTAMINE
- NMDA receptor antagonists: MEMANTINE
- Investigational: Vitamin E
- Others:
    - Anti-depressants
    - Nursing care
    - Social support
    - Memory aids

⇨ ***Alzheimer's disease is the most common cause of dementia.***

11.8.2. VASCULAR DEMENTIA

"It is a group of dementias cuased by cerebrovascular disease."

QUICK FACTS: VASCULAR DEMENTIA	
Pathology:	**Cerebrovascular disease → dementia**
Presentation:	**Cortical, sub-cortical and motor features** **Depression** **Presence of vascular risk factors**
Diagnosis:	**Neuropsychological testing** **Imaging studies**
Treatment:	**Treatment of infarction and hemorrhage** **Cholinesterase inhibitors: rivastigmine, galantamine** **NMDA antagonists: memantine**

These include:

- Mild vascular cognitive impairment(cognitive decline without affecting activities of daily living)
- Multi-infarct dementia
- Vascular dementia due to a strategic single infarct e.g. anterior cerebral infarcts, parietal infarcts
- Vascular dementia due to lacunar lesions (due to small vascular occlusions)
- Vascular dementia due to hemorrhagic lesions
- Binswanger disease or subcortical leucoencephalopathy (due to diffuse white matter disease and is due to small vessel disease as well as larger intracranial vessels)
- Subcortical vascular dementia
- Mixed Alzheimer vascular dementia

It may also be classified as cortical or sub-cortical.

RISK FACTORS:

- Hypertension, diabetes, smoking, dyslipidemia, prior cardiovascular or cerebrovascular disease

FEATURES:

Presentation is usually acute to sub-acute with deficits occurring step-wise.

- Cortical features: memory loss, visuospatial defects, language impairment, lack of insight, etc.
- Sub-cortical features: decreased concentration, forgetfulness, inertia, slowed thinking, apathy and deficits in executive functioning.
- Motor features: gait abnormalities, weakness, incoordination
- Depression

INVESTIGATIONS:

- Folstein mini-mental scoring
- Neuropsychological testing
- CT scan or MRI brain

MANAGEMENT:

- Treatment of infarction or hemorrhage
- Cholinesterase inhibitors (e.g. rivastigmine, galantamine) and NMDA antagonist (memantine) may have a role.

⇨ ***Vascular dementia is the second most common dementia after Alzheimer's disease."***

11.8.3. FRONTO-TEMPORAL DEMENTIAS (FTD)

"It is a group of dementias which predominantly affect language and personality and are characterized by gross atrophy of frontal and temporal lobes."

QUICK FACTS: FRONTO-TEMPORAL DEMENTIA	
Pathology:	**Tau-proteins, TDP-43 or FUS-gene product → neurodegenerative disease of frontal and temporal lobes**
Presentation:	**Usually 45 – 65 years old age** **Personality and behavior changes, language problems, disordered planning and organization**
Diagnosis:	**Neuropsychological assessment, imaging studies**
Treatment:	**No definite treatment**

PATHOPHYSIOLOGY:

- Neurodegenration due to tau-proteins, TDP-43 or FUS-gene product → atrophy of frontal and temporal lobes

PRESENTATION:

These usually present in a younger age as compared to other dementias (45 – 65 years).

- Personality and behavior changes
- Language problems
- Problems with planning and organization
- Spatial skills and memory are relatively preserved

INVESTIGATIONS:

- Behavioral assessment
- Neuropsyological assessment
- Imaging studies: CT scan or MRI brain, SPECT or PET scans

MANAGEMENT:

- No definite treatment
- Role uncertain: selegiline, selective serotonin reuptake inhibitors, memantine, trazodone
- Treatment of psychiatric and behavioral symptoms

11.8.4. DEMENTIA WITH LEWY BODIES (DLB)

"It is a progressive neurodegenerative disease characterized by parkinsonian features with prominent dementia, psychosis and fluctuating altered level of consciousness."

QUICK FACTS: DEMENTIAWITH LEWY BODIES	
Pathology:	**α-synuclein accumulation in brain-stem, limbic and cortical areas**
Presentation:	**Parkinsonism, fluctuating cognitive functions** **Psychiatric symptoms, dementia, extra-pyramidal features** **Autonomic dysfunction** **REM sleep behavior disorder**
Diagnosis:	**Clinical diagnosis** **Neuropsychological testing** **EEG** **Imaging studies**
Treatment:	**No definite treatment**

PATHOPHYSIOLOGY:

- Abnormal accumulation of α-synuclein protein as lewy bodies in brain-stem, limbic and cortical areas

PRESENTATION:

- Parkinsonian motor features
- Fluctuating cognitive functionse.g. excessive day-time sleep, staring into space, etc.
- Psychiatric symptoms: visual and other hallucinations, delusions
- Dementia: deficits in executive function, visuospatial impairment, less prominent anterograde memory loss
- Extra-pyramidal features
- Autonomic dysfunction e.g. orthostatic hypotension, urinary incontinence
- REM sleep behavior disorder
- Unexplained syncope
- Sensitivity to neuroleptic drugs

INVESTIGATIONS:

- Diagnosis is clinical
- Neuropsychological testing
- EEG
- CT san and MRI brain
- Exclude reversible causes of dementia

MANAGEMENT:

- No definite treatment
- Cholinesterase inhibitors – may worsen autonomic dysfunction
- NMDA antagonists
- Carbidopa/ levodopa – may worsen psychiatric or autonomic dysfunction
- Traditional and atypical neuroleptics – should not be given as these may idiosyncratic reactions like cardiac dysrhythmias

11.8.5. PROGRESSIVE SUPRA-NUCLEAR PALSY (PSP)

Aka Steele-Richardson-Olszewski syndrome

"It is a parkinson plus syndrome characterized by dementia, axial rigidity and vertical supra-nuclear gaze palsy."

PATHOPHYSIOLOGY:

- Subcortical neuronal and glial loss + tau-positive neurofibrillary tangles in basal ganglia brain-stem and frontal lobes

PRESENTATION:

- Parkinsonism, early falls, axial rigidity, wide-based gait, eye findings (blepharospasm and impaired voluntary vertical gaze)

INVESTIGATIONS:

- MRI brain may show an atrophied mid-brain "hummingbird sign"

MANAGEMENT:

- No definite treatment

11.8.6. NORMAL PRESSURE HYDROCEPHALUS (NPH)

"It is chronic communicating hydrocephalus caused by inadequate resorption or overproduction of CSF."

QUICK FACTS: NORMAL PRESSURE HYDROCEPHALUS	
Pathology:	**Inadequate resorption or over-production of CSF → communicating hydrocephalus**
Presentation:	**Triad of abnormal gait, incontinence and dementia**
Diagnosis:	**CT scan/ MRI brain** **Miller-Fisher test**
Treatment:	**Repeated spinal taps; VP shunting**

CAUSES:

- Idiopathic, ageing, prior history of subarachnoid hemorrhage, meningitis, tumor, surgery

PRESENTATION:

- Abnormal gait: broad-based, magnetic shuffling gait
- Urinary urgency, frequency or incontinence
- Dementia (sub-cortical type): memory loss, bradyphrenia

INVESTIGATIONS:

- CT scan or MRI brain: ventricular enlargement out of proportion to sulcal atrophy, peri-ventricular hyperintensity, rounded frontal horns.
- Miller Fisher test or lumbar tap test: 30 ml of CSF is removed via lumbar puncture. Improvement in cognitive performance indicates NPH.
- Serial multiple lumbar punctures
- Levodopa challenge: rules out Parkinson disease

MANAGEMENT:

- Ventriculoperitoneal shunting

⇨ ***Normal pressure hydrocephalus is characterized by a triad of abnormal gait, urinary incontinence and dementia.***

11.9. CNS NEOPLASMS

11.9.1. PRIMARY INTRACRANIAL NEOPLASMS

PRESENTATION:

- Non-specific symptoms: Headache (classically worse in morning and improves during day), cognitive changes, personality changes, gait disorder.
- Focal symptoms: These are classically sub-acute and depend on tumour location and include focal weakness, loss of vision,
- Signs:
    - Due to raised intra-cranial pressure: Papilledema
    - False localizing signs: 6th nerve palsy (due to raised ICP)
    - Focal signs: Hemiparesis, aphasia, visual field deficits
    - Seizures

INVESTIGATIONS:

- MRI brain with contrast: Imaging of choice
- CT scan brain with contrast: Patients in which MRI is contraindicated
- Additional tests: Cerebral angiogram, EEG, CSF examination

MANAGEMENT:

- First identify whether it is a primary lesion or metastases from elsewhere.

- To reduce cerebral edema: DEXAMETHASONE 12 – 16 mg/ day in divided doses PO or IV
- Anticonvulsants if seizures develop: LEVETIRACETAM, TOPIRAMATE, LAMOTRIGINE, VALPROIC ACID, LACOSAMIDE
- DVT prophylaxis for bed-bound patients
- Definitive treatment: Surgery, radiotherapy, chemotherapy (depends on tumor type)

⇨ ***Foster-Kennedy Syndrome is a presentation of frontal lobe tumors. There is ipsilateral optic atrophy due to tumor compression and papilledema in the contralateral eye because of raised ICP.***

⇨ ***Astrocytomas are the most common primary intracranial neoplasms.***

⇨ ***Most common intracranial tumours are metastatic in origin.***

⇨ ***Pilocytic astrocytomas are the most common tumours of children.***

11.9.1.1. ASTROCYTOMAS

These are neoplasms of CNS derived from astrocytes.

Table 11.18: WHO GRADING OF ASTROCYTOMAS	
GRADE I	Pilocytic astrocytoma
GRADE II	Low grade (diffuse) astrocytoma
GRADE III	Anaplastic astrocytoma
GRADE IV	Glioblastoma multiforme

PATHOPHYSIOLOGY:

- Like other tumours of CNS astrocytomas exert their effects by regional compression and invasion and may produce raised intra-cranial pressure. Focal neurological deficits and seizures may develop according to location of the tumor.

SYMPTOMS:

- The presentation is sub-acute to chronic. Symptoms may include altered mental status, cognitive impairment, headache, visual, motor or sensory impairment, seizures or ataxia.

SIGNS:

- Signs may include localizing signs (e.g. cranial nerve palsies, motor deficits) or signs of raised ICP.

MANAGEMENT:

- Includes lowering raised ICP, surgical resection, radio- and chemo-therapy depending on grade.

11.9.1.2. OLIGODENDROGLIOMAS

- Oligodendrogliomas are CNS tumours derived from oligodendrocytes.

SYMPTOMS:

- Seizures (MOST COMMON)
- Occasionally may present with headache, signs of raised ICP or focal neurological deficits. Intraventricular tumours may present with obstructive hydrocephalus.

SIGNS:

- Signs are related to involved structures.

MANAGEMENT:

- These are treated with surgery and if needed with radio- and chemo-therapy.

⇨ ***Deletion 1p 19q is associated with good chemotherapeutic response.***

11.9.1.3. EPENDYMOMAS

- Ependymomas are CNS tumours derived from ependymal cells.

PRESENTATION:

- Infratentorial ependymomas:
  - Usually grow within fourth ventricle and present as obstructive hydrocephalus, cranial nerve palsies, cerebellar dysfunction or enlarging head circumference (before suture closure).
- Supratentorial ependymomas:
  - Signs of raised ICP, changes in personality, mood and concentration, seizures, focal neurological deficit.
- Spinal ependymomas:
  - Present with progressive neurologic deficit attributable to spinal levels.

MANAGEMENT:

- Managed with surgery and radiotherapy.

11.9.1.4. PRIMARY CNS LYMPHOMAS

- Primary CNS lymphomas are extranodal, high-grade non-Hodgkin lymphomas which are confined to the CNS.
- Most of them are diffuse large B-cell lymphomas.

⇨ ***Most primary CNS lymphomas occur in immunocompromised patients e.g. AIDS, transplant recipients.***

11.9.1.5. MENINGIOMAS

- Meningiomas are CNS tumors derived from meningeal cells.

INVESTIGATIONS:

- Imaging usually shows extra-axial uniform and dense enhancement upon contrast often with a dural attachment (dural tail).

MANAGEMENT:

- Surgical resection, local radiotherapy in case of subtotal resection.

⇨ ***Meningioma is the most common primary brain tumor in adults.***

11.9.1.6. MEDULLOBLASTOMAS

- Medulloblastomas are CNS tumors derived from neural precursor cells.
- Fifty percent of them are situated in the posterior cranial fossa.
- It is managed with surgery, radiotherapy and chemotherapy.

⇨ ***Medulloblastoma is the most common malignant brain tumor in children.***

11.9.1.7. SCHWANNOMAS

- Schwannomas are CNS tumors derived from Schwann cells.
- Vestibular schwannomas (aka Acoustic neuromas) present as sensorineural hearing loss, tinnitus and vertigo.
- Management: Surgical excision.

⇨ ***Schwannomas occur most commonly in vestibular nerve.***

⇨ ***Acoustic neuroma is the most common tumor of the cerebello-pontine angle.***

Table 11.19: TUMORS OF CEREBELLO-PONTINE ANGLE (Mnemonic MEANS)
• **M**eningioma, **M**etastases • **E**pendymoma • **A**neurysm • **N**euroepithelial cyst (arachnoid cyst, epidermoid cyst) • **S**chwannoma (Most common)

11.9.2. INTRACRANIAL METASTATIC NEOPLASMS

- Metastatic tumors can involve brain parenchyma, leptomeninges or epidural space of spinal cord.
- **Brain metastases:** Lung cancer > Breast cancer > Melanoma > gastrointestinal cancers
- **Leptomeningealmetastases:** Breast cancer > Lung cancer > Melanoma > Lymphoma
- **Epidural spinal cord compression:** Breast cancer > Lung cancer > Prostate cancer > Lymphoma
- Imaging shows well-demarcated lesions often with characteristic ring-enhancement.

Table 11.20: RING ENHANCING LESIONS OF BRAIN
Tuberculoma (most common in developing countries)
Toxoplasmosis (most common worldwide)
Brain abscess
Sarcoidosis
Granulomas
Demyelinating lesions
Primary brain tumors
Metastatic tumors in brain
Radiation necrosis
Lymphoma
Stroke
Intra-cranial hemorrhage

11.9.3. INTRASPINAL NEOPLASMS

Table 11.21: EXAMPLES OF SPINAL CORD TUMORS		
Intramedullary	**Intra-dural extramedullary**	**Extradural extramedullary**
Ependymoma Astrocytoma	Meningioma Schwannoma Neurofibroma	Metastases (lung, breast, prostate, GIT) Primary bone lesions (e.g. multiple myeloma)

11.10. IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

Aka Benign intracranial hypertension (BIH) or pseudotumor cerebri

"It is a syndrome of raised intracranial pressure of unknown etiology."

RISK FACTORS:

- Obesity, females of reproductive age, excessive intake of vitamin A, some medications (e.g. tetracycline), obstructive sleep apnea, transverse cerebral venous sinus stenosis

PRESENTATION:

- Headache (global, worse in morning); visual changes (visual field defects including progressive loss of peripheral vision or blind spots, diplopia); pulsatile tinnitus; radicular pain

INVESTIGATIONS:

- Ophthalmoscopy: papilledema
- Perimetry for visual fields

MANAGEMENT:

- General: weight loss, salt restriction
- Medical: ACETAZOLAMIDE
- Surgery: VP shunting, optic nerve sheath fenestrations

11.11. MOVEMENT DISORDERS

"These are clinical syndromes of excess or paucity of voluntary or involuntary movements."

Table 11.22: MOVEMENT DISORDERS

Tremors	Rapid alternating contractions of agonist and antagonist muscles in an oscillating, rhythmic manner.
Athetosis	Slow, convoluted, writhing, involuntary movements of distal parts of limbs e.g. arms, hands, feet.
Dystonias	Involuntary patterned sustained or repeated muscle contractions associated with twisting and abnormal posture.
Hemiballismus	Wide flinging incessant movemnts which occur on one side of body.
Chorea	Sudden brief spontaneous involuntary but semi-purposeful jerky movements.
Myoclonus	Sudden involuntary isolated purposeless jerking of a muscle or a group of muscles.
Tics	Sudden repetitive non-rhtyhmic motor movement or vocalization involving discrete muscle group which can be suppressed at will.
Stereotypy	Repetitive or ritualistic movement, posture or utterance.

11.11.1. ESSENTIAL TREMORS

"It is an autosomal dominant disorder in which there are slowly progressive tremors in upper limbs and other parts of body."

PRESENTATION:

Tremors:

- Fine amplitude, high frequeny postural tremors in upper limbs.
- May also occur in head (titubation), voice, jaws, lips and face.
- Tremors worsen with interntional activity, emotion, hunger and fatigue.
- Tremors subside/ reduce by relaxing body part, taking ethanol and during sleep.
- Distorted hand-writing
- Absence of other abnormalities e.g. bradykinesia, rigidity, etc.

INVESTIGATIONS:

- Electrolytes, thyroid function tests, creatinine, liver function tests, serum ceruloplasmin.

MANAGEMENT:

- Reassurance in mild cases
- Propranolol or primidone

⇨ ***Essential tremor is the most common movement disorder.***

11.11.2. PARKINSON DISEASE

"It is a progressive neurodegenerative disease in which there is loss of dopamine-secreting neurons in basal ganglia and leads to bradykinesia, tremors and rigidity."

QUICK FACTS: PARKINSON'S DISEASE	
Pathology:	**Degeneration of dopaminergic neurons in substantia nigra → dereased dopaminergic and increased cholinergic output to striatum**
Presentation:	**Tremors, bradykinesia, rigidity, postural instability** **Shuffling and festinating gait** **Mask facies, stooped posture, micrographia**
Diagnosis:	**Clinical diagnosis**
Treatment:	**MAO-B inhibitors, dopamine agonists, levodopa, COMT inhibitors, anticholinergics, amantadine**

PATHOPHYSIOLOGY:

- Degeneration of dopaminergic neurons in substantia nigra (with presence of Lewy bodies composed of α-synuclein) → imbalance between dopaminergic and cholinergic output to striatum → increases inhibitory output from these structures

PRESENTATION:

- Tremors:
  - Usually resting tremor (pill-rolling movements) which decreases with movement.
  - In early disease tremor can be unilateral or intermittent and starts in hands.
  - Usually high amplitude and low frequency (3 – 7 Hz).
- Bradykinesia:
  - Slowness of movement specially while performing tasks such as buttoning, tying shoe-laces.
- Rigidity:
  - There is increased resistance to passive movements around joints.
  - Cog-wheel rigidity: resistance is ratchet-like jerky and is due to tremors superimposed on rigidity.
  - Lead-pipe rigidity: resistance is smooth throughout the range of motion.
  - Also: decreased arm-swing while walking, stiffness in stooped posture.
- Postural instability:
  - There are impaired postural reflexes usually in late disease.
  - There is feeling of imbalance, tendency to fall and eventually patient becomes wheelchair-bound.
  - Stooped posture
  - Positive pull test: patient unable to maintain balance when pulled from behind.
- Gait disorders:
  - Shuffling gait with short steps, difficulty initiating first step.
  - Festinating gait: patient walking with short steps having tendency to fall forwards, compensates by taking rapid steps.
  - Freezing/ sudden halt of movements
- Other features:
  - Motor: mask facies, decreased blinking, hypophonia, palilalia, impaired upward gaze, micrographia, dysarthria, dysphagia.
  - Cognitive: cognitive dysfunction and dementia (usually late)
  - Sleep disturbances
  - Psychiatric features: depression, apathy
  - Autonomic dysfunction:orthostatic hypotension, constipation, increased sweating/ sebum.
- Progression:
  - Usually leads to significant disability in 5 – 10 years.
  - Death usually occurs due to respiratory infections.

INVESTIGATIONS:

- Diagnosis is clinical.
- MRI or SPECT scans may be done for ruling out differentials.
- Rule out Wilson disease if features appear in <40 years of age.
- Look for features of Parkinson plus syndromes.

MANAGEMENT:

- Symptomatic therapy:
  - Monoamine oxidase B (MAO-B) inhibitors:
    - Used as early treatment in mild symptoms.
    - Side effects: dyskinesias, nausea, abdominal pain, dry mouth
    - Examples: SELEGILINE 5 – 10 mg daily, RASAGILINE 1 mg daily
  - Dopamine agonists:
    - Used as early treatment in moderate symptoms. These can delay need for levodopa.
    - Usually used in younger patients or in healthy older patients.
    - Side effects: more sleepiness, hallucinations, edema, impulse control disorders, less motor fluctuations or dyskinesias
    - Examples: ROPINIROLE, PRAMIPEXOLE, BROMOCRIPTINE, ROTIGOTINE, APOMORPHINE
  - LEVODOPA: gold standard treatment
    - Improves bradykinesia, rigidity and tremors.
    - CARBIDOPA or BENSERAZIDE is added to inhibit conversion of levodopa to dopamine in systemic circulation.
    - Combination is available as immediate-release and extended-release forms.
    - Avoided as initial therapy unless symptoms are severe or patients are older with cognitive impairment.
    - Side-effects: nausea, vomiting, agitation, somnolence, hallucinations. Long-term use leads to motor fluctuations (end-of-dose akinesia, on-off episodes) and dyskinesias.
    - It should be taken on an empty stomach or at least one hour after meals.
    - Available as CARBIDOPA/LEVODOPA immediate release 25/250 tablets or 25/100 extended release tablets. Starting dose is around 100 mg three to four times daily for LEVODOPA IR (maximum 800 mg/ day) or 200 mg twice daily for LEVODOPA ER (maximum 1600 mg/ day). Carbidopa should not exceed >200 mg per day.
  - Catechol-O-methyl transferase (COMT) inhibitors:
    - Prolong the effect of levodopa and used as an adjunctive treatment.
    - Examples: ENTACAPONE, TOLCAPONE
  - Anticholinergic agents:
    - Improve tremors but less useful for bradykinesia or rigidity.
    - Examples: TRIHEXYPHENIDYL, BENZTROPINE
  - Amantadine:
    - Unclear mechanism of action
    - Side effects: nausea, headache, confusion, hallucinations
  - DEEP BRAIN STIMULATION:
    - Used in patients whose motor fluctuations and dyskinesias are not controlled with medical therapy.
  - Thalamotomy or pallidotomy for refractory patients.
- Neuroprotective/ disease-modifying therapy:
  - At present this is investigational.
  - MAO-B inhibitors, levodopa, dopamine agonists and amantadine may have neuroprotective activity.
- Management of other associated features:
  - Dementia: rivastigmine, donepezil
  - Depression
  - Hallucinations or delusions: selective serotonin inverse agonists, antipsychotics (quetiapine)
  - Sleep hygiene
  - Physical therapy, speech therapy

⇨ ***Cardinal features of Parkinson disease = tremor + bradykinesia + rigidity + postural instability***

⇨ ***Most common initial presentation in PD is unilateral resting tremor of upper limb.***

⇨ ***Parkinson plus syndromes include:***

Shy-Dragger syndrome or Multiple System Atrophy: Parkinson disease + autonomic dysfuntion + ataxia
Progressive supra-nuclear palsy: Parkinson disease + supranuclear ophthalmoplegia + pseudobulbar palsy
Diffuse Lewy body disease: visual hallucinations + early dementia + Parkinson disease
Corticobasal degeneration: Parkinson disease + progressive dementia + limb apraxia

11.11.3. HUNTINGTON'S CHOREA

"It is an autosomal dominant trinucleotide repeat disorder characterized by chorea and dementia."

PATHOPHYSIOLOGY:

- Trinucleotide CAG repeats in huntingtin gene → underactiviy of GAB and ACh or over-acitivity of dopamine

PRESENTATION:

- It presents between 30 – 50 years of age and manifestations worsen progressively

INVESTIGATIONS:

- CT or MRI brain: cerebral atrophy particularly caudate nucleus

MANAGEMENT:

- Management is symptomatic.
- TETRABENAZINE
- RESERPINE
- Dopamine antagonists e.g. phenothiazines, haloperidol
- Amantadine
- Deep brain stimulation

11.12. DEMYELINATING DISEASES

11.12.1. MULTIPLE SCLEROSIS

"It is a chronic inflammatory immune-mediated demyelinating disorder affecting the central nervous system."

QUICK FACTS: MULTIPLE SCLEROSIS	
Pathology:	**Unknown trigger → CD8+ mediated destruction of oligodendrocytes and myelin → gliosis**
Presentation:	**Recurrent attacks of focal neurological deficits e.g. paresthesias and pains, weakness, vision loss, ataxia**
Examination:	**Relevant examination**
Diagnosis:	**MRI brain with gadolinium contrast shows white matter lesions** **CSF examination** **Evoked potentials**
Treatment:	**Acute attacks: steroids, IVIG, plasmapharesis** **Immunomodulators**

PATHOPHYSIOLOGY:

- Unknown etiology (genetic, environmental, infectious, low vitamin D)→activate toll-like receptors on dendritic cells →migrate across blood-brain barrier and activate T and B cells → secrete

cytokines → antigen presenting cells present antigens to T cells → destruction of oligodendrocytes and myelin by CD8+ cell response, helper T cells secreting interleukins and polyclonal antibodies by B cells → eventual death/ injury of neurons → gliosis.

PRESENTATION:

- Recurrent attacks of focal neurological dysfunction, which recover over weeks to months.
- Usually occurs in young females.
- Deficits are worsened by exercise, heat or fatigue.
- WHITE MATTER LESIONS ARE SAID TO BE DISSEMINATED IN SPACE AND TIME.
- A single attack (clinically isolated syndrome) does not classify as MS. For diagnosis there has to be at least two attacks at least six months apart.

Deficits include:

- Sensory: paresthesias, hypesthesias or pains in limbs
- Motor (usually pyramidal): weakness, spasticity, loss of tendon reflexes.
- Visual:
    - Optic neuritis presents as central scotoma, retro-orbital pain aggravated by movements, disturbed color perception, and afferent pupillary defect.
    - *Inter-nuclear ophthalmoplegia (INO)*occurs due to lesion in medial longitudinal fasciculus. It presents as diplopia, nystagmus. On lateral gaze, there is failure of adduction in ipsilateral eye and development of nystagmus in contralateral eye.
- Cerebellar: ataxia, intention tremor, dysarthria, nystagmus
- Cerebral: memory loss, personality change, emotional lability, depression
- Spinal UMN (transverse myelitis):
    - Loss of bowel or bladder control
    - Sexual dysfunction
    - Lhermitte's phenomenon: shock like sensation evoked by neck flexion.
- Autonomic: impotence, constipation
- Others: fatigue, neuropathic pain, Uhthoff's phenomenon (symptoms worsened by heat), trigeminal neuralgia, bilateral facial paralysis, facial myokymia, rarely seizures.

DISEASE COURSE:

- Relapsing-remitting (RRMS):
    - Most common variety.
    - There are exacerbations of disease with little or no progression in between.
- Secondary progressive (SPMS):
    - Initially starts as RRMS but gradually progresses.
- Primary progressive MS (PPMS):
    - There is gradual progression of disability without any distinct exacerbations.
- Progressive-relapsing MS (PRMS):
    - Initially starts as PPMS but later develops distinct exacerbations.
- Clinically silent/ benign:
    - Asymptomatic stable plaques.

INVESTIGATIONS:

- MRI with gadolinium contrast (usually T2 and FLAIR images):
    - Hyperintense small ovoid white matter lesions usually peri-ventricular and oriented perpendicularly (Dawson fingers).
    - Acute lesins may have surrounding edema.
- CSF: mild lymphocytic pleocytosis, presence of oligoclonal bands, elevated IgG, normal total proteins
- Visual, auditory and somatosensory evoked potentials: identify silent lesions
- Others: urodynamic studies

MANAGEMENT:

Specific treatment:

- Acute attacks:
    - High dose METHYLPRENISOLONE 1 g iv for 3 – 5 days
    - IV IMMUNOGLOBULINS (IVIG) or plasmapharesis in steroid refractory cases

- Immunomodulatory/ disease-modifying agents for MS (DMAMS) for relapses:
    - Interferon-ß1a, Peginterferon- ß1a, Interferon-ß1b, Glatiramer acetate, Natalizumab, Fingolimod, Mitoxantrone, Cladribine, Teriflunomide, Dimethylfumarate, Alemtuzumab, Daclizumab
- Immunomodulatory/ disease-modifying therapy for progressive disease:
    - Mitoxantrone, Methotrexate, Azathioprine, Cyclophosphamide, Rituximab

Symptomatic treatment:

- Muscle spasticity: BACLOFEN, DANTROLENE, TIZANIDINE, DIAZEPAM
- Neuropathic pain: Tricyclic antidepressants, GABAPENTIN, CARBAMAZEPINE
- Bladder dysfunction:
    - Hyper-reflexia: frequent voiding, evening fluid restriction, OXYBUTININ
    - Hypo-reflexia: BETHANECHOL
    - Dyssynergia: anti-cholinergics, intermittent catheterizations
- Depression: anti-depressants
- Fatigue: AMANTADINE, METHYLPHENIDATE
- Sexual dysfunction: oral phosphodiesterase-5 inhibitors e.g. SILDENAFIL, TADALAFIL

Table 11.23: 2017 MC DONALD CRITERIA FOR DIAGNOSIS OF MULTIPLE SCLEROSIS
DIS = disseminate in time, DIT = disseminated in space

CLINICAL PRESENTATION	ADDITIONAL CRITERIA NEEDED FOR DIAGNOSIS
IN A PERSON WITH A TYPICAL ATTACK	
≥2 attacks with ≥2 lesions Or ≥2 attacks with ≥1 lesion and historical evidence of a lesion in separate location	None
≥2 attacks with ≥1 lesion	Any one of following: • DIS: Additional clinical attack at a different site • DIS: ≥1 typical T2 lesion in ≥2 areas of CNS: periventricular, juxta-cortical/cortical, infratentorial or spinal cord (symptomatic or asymptomatic)
1 attack with ≥2 lesion	Any one of following: • DIT: Additional clinical attack at a different site • DIT: Simultaneous presence of both enhancing and non-enhancing MRI lesions (symptomatic or asymptomatic) • DIT: New T2 or enhancing MRI lesion compared to baseline scan • CSF-specific oligoclonal bands
IN A PERSON WITH AN ATYPICAL ATTACK	
1 attack with 1 lesion	Any one of following: • DIS: Additional clinical attack at a different site • DIS: ≥1 typical T2 lesion in ≥2 areas of CNS: periventricular, juxta-cortical/cortical, infratentorial or spinal cord (symptomatic or asymptomatic) AND one of these: • DIT: additional clinical attack • DIT: simultaneous presence of both enhancing and non-enhancing MRI lesions (symptomatic or asymptomatic) • DIT: New T2 or enhancing MRI lesion compared to baseline scan • CSF-specific oligoclonal bands
IN A PERSON WITH PROGRESSION FROM ONSET	
Progression from onset	• 1 year of disability progression AND two of the following: • ≥1 typical T2 lesion: periventricular, juxta-cortical/cortical, infratentorial or spinal cord (symptomatic or asymptomatic) • ≥2 T2 spinal cord lesions • CSF-specific oligoclonal bands

11.12.2. OTHER DEMYELINATING DISEASES

11.12.2.1. NEUROMYELITIS OPTICA

Aka Devic's disease

- A clinical variant of MS.
- Separate attacks of optic neuritis with longitudinally extensive myelitis.
- MRI brain is usually normal whereas MRI spine shows enhancing lesions extending for more than three segments of spinal cord.
- Antibody against aquaporin-4 channel is present in 50%.
- Acute attacks are treated just like MS.
- Mycophenolate mofetil, rituximab or azathioprine + glucocorticoids are used to prevent relapses.

11.12.2.2. MARBURG'S DISEASE

Aka acute MS

- A clinical variant of MS.
- Acute attack is followed by a fulminant course leading to death within 1 – 2 years.
- Typical MS therapies are ineffective.

11.13. WERNICKE'S ENCEPHALOPATHY AND KORSAKOFF'S PSYCHOSIS

"This is a complex of neurological conditions caused by deficiency of thiamine."

RISK FACTORS:

- Chronic alcoholism, malnutrition, hyperemesis gravidarum, prolonged parenteral nutrition, severe anorexia nervosa, malignancies, immunodeficiency syndromes, liver disease, bariatric surgery

PATHOPHYSIOLOGY:

- Deficiency of thiamine →disturbed Krebs cycle and pentose phosphate pathway →neuronal death in mammillary bodies, thalamus (Wernicke syndrome)

PRESENTATION:

Wernicke's encephalopathy is acute to sub-acute and presents as:

- Ocular findings:nystagmus, ophthalmoplegia (due to cranial nerve palsies)
- Mental status changes: confusion, delirium, coma
- Cerebellar dysfunction: ataxic gait
- Others: hypotension, peripheral neuropathy

Korsakoff psychosis is usually irreversible:

- Retrograde and anterograde amnesia
- Confabulation

INVESTIGATIONS:

- CBC, electrolytes, lactate, magnesium
- Serum or urine toxicology screen
- MRI brain

MANAGEMENT:

- IV thiamine replacement 50 – 100 mg daily
- Be careful not to give dextrose before thiamine in these patients as it can worsen neurological symptoms
- Simultaneous replacement of magnesium and other vitamins

⇨ ***Wernicke encephalopathy is associated with a triad of confusion, ocular findings (), cerebellar dysfunction.***

11.14. TRAUMATIC CNS INJURY

Trauma to head may lead to:

- Concussion and diffuse axonal injury
- Skull fracture
- Cerebral edema
- Cerebral contusion
- Subdural hematoma
- Epidural hematoma
- Subarachnoid hemorrhage

11.14.1. EPIDURAL HEMATOMA

"It is collection of blood in the epidural space."

QUICK FACTS: EPIDURAL HEMATOMA	
Pathology:	**Rupture of meningeal artery or dural sinus (direct blow)**
Presentation:	**Loss of consciousness or lucid interval** **False localizing signs**
Diagnosis:	**CT scan brain: hyperdense biconvex or lens-shaped lesion which does not cross suture lines**
Treatment:	**Surgical drainage (Burr-hole)**

PATHOPHYSIOLOGY:

- Direct blow to skull (usually in young adults) → tearing of meningeal artery or dural sinus

PRESENTATION:

- Loss of consciousness
- Lucid interval (patient conscious and alert after injury but develops unconsciousness after few hours)
- False localizing signs

INVESTIGATIONS:

- CT brain: biconvex or lens-shaped hyperdensity/ collection in epidural space which does not cross suture lines

MANAGEMENT:

- Evacuation and repair

11.14.2. SUBDURAL HEMATOMA

"It is collection of blood in the subdural space."

QUICK FACTS: SUBDURAL HEMATOMA	
Pathology:	**Rupture of bridging veins in subdural space (risk in infants, elderly, alcoholics, patients with dementia or those on anti-coagulation)**
Presentation:	**Loss of consciousness or lucid interval** **False localizing signs**
Diagnosis:	**CT scan brain hyperdense (acute) or hypodense (chronic) crescent-shaped lesion which crosses suture lines**
Treatment:	**Surgical drainage (Burr-hole)**

PATHOPHYSIOLOGY:

- Rupture of briding veins in the subdural space as a result of movement of brain within the skull
- Patients with widening of distance between dura mater and arachnoid mater are at risk e.g. elderly, alcoholics, dementia, and infants. Other at risk patients are those on anticoagulation.

PRESENTATION:

- It may be acute (<72 hours) or chronic (>21 days)
- Acute:
    - Loss of consciousness or lucid interval
    - False-localizing signs: 6th nerve palsy, contralateral dilated pupil, ipsilateral hemiparesis)
- Chronic:
    - Often with or without history of trauma which may be mild

INVESTIGATIONS:

- CT brain:
    - Crescent-shaped hyperdensity/ collection in subdural space which can cross suture lines (acute)
    - Hypodensity in same manner (chronic)

MANAGEMENT:

- Surgical drainage e.g. Burr hole craniostomy

⇨ ***It is the most common cause of traumatic intra-cranial mass lesion.***

11.14.2. SUBARACHNOID HEMORRHAGE

See 11.5.4.

11.15. DEGENERATIVE MOTOR NEURON DISEASES (MND)

"Motor neuron diseases are a group of diseases characterized by degeneration of motor neurons and sparingof sensory neurons."

TYPES OF MND:

- Amyotrophic lateral sclerosis (ALS)
- Progressive bulbar palsy (PBP)
- Progressive muscular atrophy (PMA)
- Primary lateral sclerosis (PLS)
- Kennedy's disease

PATHOPHYSIOLOGY:

- There is degeneration of motor neuron cells i.e. anterior horn cells of spinal cord, motor nuclei of lower cranial nerves, and corticospinal and corticobulbar pathways.
- These diseases present with progressive muscle weakness with wasting, loss of reflexes and muscle tone.
- Bulbar, cervical, thoracic and lumbosacral segments are involved.

⇨ ***Amyotrophic lateral is the most common form of motor neuron disease.***

11.15.1. AMYOTRPHIC LATERAL SCLEROSIS (ALS)

Aka Lou Gehrig's disease/ Classical MND

QUICK FACTS: AMYOTRPHIC LATERAL SCLEROSIS	
Pathology:	**Degeneration of both upper and lower motor neurons**
Presentation:	**Progressive weakness of lower limbs with wsting with loss of reflexes and spasticity, stumbling and falling** **Reduced skilled tasks with hands, stiffness, weakness** **Bulbar features: slurred speech, hoarse voice, drooling, choking** **Pseudobulbar affect: emotional lability**
Diagnosis:	**Clinical diagnosis** **EMG: partial denervation, reduced CMAP** **Muscle biopsy: denervated muscle**
Treatment:	**Riluzole** **Supportive treatment**

- It affects both upper and lower motor neurons at 2 or more levels.
- It can be inherited or sporadic.

PRESENTATION:

- Symptoms begin usually in lower limbs. There is progressive muscle weakness, wasting, loss of reflexes and muscle tone leading to problems in the involved segment (cervical, thoracic and lumbosacral). Bulbar involvement is present in 20 – 25%.
- Lower limbs: frequent stumbling and falling especially on increasing pace, abnormal gait due to foot drop, muscle cramps
- Upper limbs: reduced skilled tasks with hands, stiffness, weakness, wasting and wrist drop
- Bulbar features: slurred speech, hoarseness of voice, drooling, choking/ aspiration while eating.
- Normal bowel and bladder control, sensations and extra-ocular functions.
- Pseudo-bulbar affect: emotional lability e.g. inadequate laughing or crying, depression
- Dementia: some patients develop a frontotemporal like dementia
- Parkinsonism in some patients

INVESTIGATIONS:

- EMG: chronic partial denervation with abnormal activity in resting muscle, reduced CMAP
- Muscle biopsy: denervated muscle
- Creatine kinase: normal or slightly elevated

MANAGEMENT:

- RILUZOLE 50 mg orally twice daily
    - Reduces pre-synaptic release of inhibitory glutamate
    - Only increases survival by 2 – 3 months.
- Nutrition:
    - Good enteral nutrition
    - If unable to take orally then nasogastric intubation or PEG
- Non-invasive ventilation in patients with persisting hypoxia and nocturnal hypoventilation
- Tracheostomy may be considered
- Secretions and drooling: anticholinergic drugs, suction
- To improve mobility: braces or walker
- Spasticity: physical therapy, anti-spasmodic drugs

11.15.2. OTHER MOTOR NEURON DISEASES

11.15.2.1. PROGRESSIVE BULBAR PALSY

- The lowest motor neurons of brain-stem are affected.
- It leads to slurred speech, dysphagia and difficulty chewing.

11.15.2.2. PSEUDO-BULBAR PALSY

- There is bilateral corticobulbar disease causing upper motor neuron dysfunction.
- There is emotional lability i.e. inadequate laughter or crying on seemingly lesser stimuli (pseudo-bulbar affect).

11.15.2.3. PRIMARY LATERAL SCLEROSIS

- It affects the upper motor neurons.
- Weakness mainly occurs in the lower limbs.

11.15.2.4. PROGRESSIVE MUSCULAR ATROPHY

- It affects mainly lower motor neurons i.e. anterior horn cells of spinal cord.
- It mainly causes weakness/ clumsiness of hands.

11.16. NON-TRAUMATIC DISORDERS OF SPINAL CORD

Spinal cord syndromes include:

- Complete transverse cord lesion:
    - Loss of all sensations below the lesion
    - Loss of power below the lesion
    - Radicular pain or segmental paraesthesia at the level of lesion
    - Loss of reflexes below the level of lesion.
    - Cervical lesions may lead to loss of sympathetic supply e.g. bradycardia, hypotension
    - C3-5 lesions may cause diaphragmatic paralysis.
    - Chronic slowly developing lesions may cause increased reflexes below the lesion.
    - Examples: whiplash injury, transverse myelitis, disc herniation
- Hemisection of spinal cord (Brown-Sequard syndrome):
    - Loss of contralateral pain and temperature sensations below the lesion.
    - Loss of ipsilateral joint position and vibration sense below the lesion.
    - Preservation of touch sensation.
    - Segmental flaccid paralysis at the level of lesion.
    - Ipsilateral spastic paralysis below the level of lesion.
    - Examples: traumatic lesions, multiple sclerosis
- Central cord syndrome:
    - Dermatomal loss of pain and temperature at the level of lesion with preserved touch sensations (dissociated sensory loss).
    - Dermatomal loss of pain and temperature sensations above and below the lesion causing an upper and a lower level (suspended sensory loss).
    - Bilateral loss of power below the level of lesion (upper limbs >lower limbs, Distal muscles > proximal muscles).
    - Examples: syringomyelia, hematomyelia, intra-medullary tumor
- Anterior cord syndrome:
    - Usually starts with severe back pain at the level of lesion.
    - Usually have bladder dysfunction (urinary retention).
    - Bilateral loss of pain and temperature below the level of lesion.
    - Preserved joint position and vibration sense.
    - Bilateral loss of motor function below the level of lesion.

    - Incomplete syndromes may have paralysis with sensory or bladder dysfunction.
    - Examples: anterior spinal artery infarction, disc herniation
- Posterior column syndrome:
    - Dermatomal loss of position and vibration sense below the level of lesion with preserved pain, touch, temperature and motor function.
    - Sensory ataxia
    - Positive Romberg's test
    - May have bladder dysfunction
    - May have Lhermitte's phenomenon
    - Examples: subacute combined degeneration of cord, tabes dorsalis, Friedrich's ataxia, epidural metastases, multiple sclerosis
- Conus medullaris syndrome:
    - Bladder and rectal dysfunction
    - Loss of sexual function
    - Saddle anesthesia
    - Absent bulbocavernosus reflex
    - Upper or lower motor neuron deficits of gluteus muscles
    - Examples: trauma, disc herniation, tumors
- Cauda equina syndrome:
    - Bowel and bladder dysfunction
    - Saddle anesthesia
    - Lower motor neuron type leg weakness and sensory loss
    - Examples: disc herniation, arachnoiditis, tumor, lumbar spinal stenosis

11.16.1. SUB-ACUTE COMBINED DEGENRATION OF CORD

Aka Lichteim's disease

"It is a chronic neurodegenerative disorder caused by deficiency of vitamin B12."

QUICK FACTS: SUBACUTE COMBINED DEGENERATION OF CORD	
Pathology:	**Vitamin B12 deficiency → impaired spinal cord myelinization**
Presentation:	**Dorsal column: Loss of vibration and position sense in lower limbs and occasionally upper limbs** **Lateral column: paresthesias** **Absent ankle jerk, brisk knee jerk, upgoing plantars** **Other features of vitamin B12 deficiency**
Diagnosis:	**Clinical diagnosis** **Features of B12 deficiency** **Somatosensory and motor evoked potentials, NCVs, MRI spine**
Treatment:	**Cyanocobalamin**

CAUSES:

- Vitamin B12 deficiency, vitamin E deficiency, copper deficiency, nitrous oxide abuse

PATHOPHYSIOLOGY:

- Deficiency of vitamin B12 →increased methylmalonyl coA→ impairs spinal cord myelinization especially dorsal and lateral columns → impaired nerve transmission

PRESENTATION:

- Features of dorsal column involvement: dysesthesias and loss of vibration and position sense in lower limbs and often in upper limbs
- Features of lateral column involvement: paresthesias
- Other features:
    - Absent ankle jerks, brisk knee jerks and upgoing plantars
    - Lhermite phenomenon: flexion of neck produces electric-shock like sensations in arms or lower spine

- Associated features of vitamin B12 deficiency: anemia, optic atrophy, peripheral neuropathy

INVESTIGATIONS:
- CBC: may show features of vitamin B12 deficiency or may be normal
- Tests for B12 deficiency: low vitamin B12, raised methylmalonic acid and homocysteine
- Somatosensory-evoked potentials: abnormal
- Motor-evoked potentials: abnormal
- Nerve conduction studies: peripheral neuropathy
- MRI spine: hyperintense signals in posterior and lateral columns in T2-weighted images

MANAGEMENT:
- CYANOCOBALAMIN 1 mg IM once daily for 7 – 12 days followed by 1 mg once weekly for 4 weeks and then 1 mg every 1 – 3 months for life.

11.16.2. MYELITIS

"It is inflammation of the spinal cord."

CAUSES:
- Infectious: herpes simplex, herpes zoster, CMV, EBV, enteroviruses, AIDs, polio virus, mycoplasma, Lyme disease, TB
- Non-infectious: multiple sclerosis, neuromyelitis optica, SLE, sarcoidosis, vaccinations (hepatitis B, MMR)
- Idiopathic

PATHOGENESIS:
- Inflammation of spinal cord → damage to myelin and axons
- Leukomyelitis: inflammation of white matter
- Poliomyelitis: inflammation of gray matter
- Transverse myelitis: both gray and white matter

PRESENTATION:
- Features of spinal cord transection

INVESTIGATIONS:
- MRI brain
- MRI spine with contrast enhancement
- CSF examination

MANAGEMENT:
- Supportive management
- Treat underlying causes e.g. acyclovir for VAZ, CMV, etc.
- Immunomodulators e.g. steroids

11.16.3. SPINAL EPIDURAL ABSCESS

"It is an abscess in epidural space of spinal cord."

PATHOGENESIS:
- Direct infection (local infections e.g. vertebral osteomyelitis or inoculation e.g. local procedure) OR hematogenous spread → epidural infective focus → local abscess formation → presents as spinal cord lesion with features of infection

PRESENTATION:
- Fever + back pain + progressive neurological deficits below the level of lesion

INVESTIGATIONS:

- CBC: neutrophilia
- ESR: raised
- CSF: neutrophilia, increased proteins, normal glucose
- MRI with contrast: diagnostic

MANAGEMENT:
- Antibiotics for up to 2 months
- Surgical decompression and drainage

11.16.4. SYRINGOMYELIA

"It is a fluid-filled cavity or syrinx within the spinal cord."

QUICK FACTS: SYRINGOMYELIA	
Pathology:	**Cavity formation in spinal cord → interrupts decussating spinothalamic fibers**
Presentation:	**Loss of pain and temperature in upper limbs with weakness and atrophy of hand, impaired bowel and bladder features, Horner's syndrome**
Diagnosis:	**MRI, myelography**
Treatment:	**Surgical decompression**

- Syringobulbia is a similar cavity within the brain-stem.

PATHOPHYSIOLOGY:
- Syrinx interrupts decussating spinothalamic tracts carrying pain and temperature → loss of these sensations → syrinx enlarges → further sensations may be disturbed e.g. position and vibration sense or may compress anterior horn cells

PRESENTATION:
- Sensory loss:
  - Loss of pain and temperature in upper limbs and shoulders (shawl-like pattern)
- Motor loss:
  - Weakness and atrophy of hands muscles which progresses upwards
- Autonomic:
  - Impaired bowel and bladder functions and sexual functions, Horner's syndrome
- Extension into medulla:
  - Dysphagia, nystagmus, tongue atrophy, loss of sensations in trigeminal area
- Others:
  - Charcot's joints, neuropathic ulcers

INVESTIGATIONS:
- MRI
- Myelography
- Somatosensory evoked potentials

MANAGEMENT:
- Surgical decompression by laminectomy, myelotomy, or shunts
- Neurorehabilitation

11.17. PERIPHERAL NEUROPATHIES

"It is defined as a disease of injury of peripheral sensory, motor or autonomic nerves."

PATHOPHYSIOLOGY:

- Peripheral nerves are composed of a central axon and external insulation called myelin.

Nerves can be injured by:

1. Damage to cell body (neuronopathy)
2. Damage to axon at some point (Wallerian degeneration)
3. Diffuse damage to axon (axonal degeneration)
4. Segmental injury to myelin sheath without injury to neuron (demyelination)

According to distribution it may be of following types:

- Mononeuropathy: involvement of a single nerve
- Polyneuropathy: symmetrical involvement of multiple nerves
- Mononeuropathy multiplex: involvement of multiple nerves in an asymmetrical fashion

There are two broad categories according to type of damage:

- Demyelinating:
  - There is disruption of myelin sheath which interferes with saltatory conduction.
  - It is usually acute or subacute in presentation.
  - It involves distal as well as proximal neurons.
  - It causes slow nerve conduction velocity or in severe cases conduction block. There is no fibrillation on EMG.
  - It usually does not cause muscle wasting.
  - Motor involvement is greater than sensory involvement.
  - There is global areflexia from the onset.
- Axonal:
  - There is damage to long axons of nerves.
  - It is usually of gradual and insidious onset.
  - It usually involves distal neurons.
  - Nerve conduction is normal or slightly slowed. There is reduced or absent action potential (amplitude). Fibrillation is prominent.
  - Muscle wasting is common.
  - There is significant sensory involvement.
  - Ankle reflex is lost early while proximal reflexes are relatively preserved.

⇨ ***Most common cause of mononeuropathy is carpal tunnel syndrome.***

⇨ ***Most common cause of polyneuropathy is diabetes mellitus (developed countries) or leprosy (developing countries).***

11.17.1. POLYNEUROPATHIES

"These are neuropathies with involvement of multiple nerves in a symmetric pattern."

CAUSES:

See table

Polyneuropathies can be predominantly motor, sensory or mixed.

- Pure motor::
  - Alcoholism, diabetes, hypothyroidism, uremia, amyloidosis, leprosy, lyme disease, HIV, sarcoidosis, vasculitis, vitamin B12 deficiency, drugs (isoniazid, metronidazole, hydralazine, flecainide), lymphoma
- Pure sensory:
  - Porphyria, lead toxicity, diphtheria, CIDP, GBS, drugs (dapsone)
- Mixed:
  - Alcoholism, diabetes, hypothyroidism, uremia, sarcoidosis, vasculitis, paraneoplastic, CIDP, GBS, hereditary motor and sensory neuropathies (e.g. Charcot-Marie-Tooth disease), drugs (vincristine, vinblastine, paclitaxel, cisplatin, nitrofurantoin, amiodarone, allopurinol)

INVESTIGATIONS:

- Nerve conduction studies
- Initial tests: CBC, ESR, blood sugar, LFTs, urea, creatinine, serum vitamin B12, paraproteins, thyroid function tests, vasculitis profile
- Other tests: CSF examination, nerve biopsy

MANAGEMENT:

- Manage underlying cause.
- Neuropathic pain relief:
  - Simple analgesics e.g. ASPIRIN, NSAIDs
  - GABAPENTIN 300 – 1200 mg orally three times daily
  - PREGABALIN 50 – 100 mg orally three times daily
  - SNRIs: DULOXETINE, VENLAFAXINE
  - Tricyclic anti-depressants e.g. AMITRIPTYLINE 10 – 150 mg orally at night
  - Tricyclic antidepressants
- Autonomic dysfunction:
  - See section on dysautonomias
- Physical therapy and splints to prevent contractures

Table 11.24: CAUSES OF POLYNEUROPATHIES

	Acute	Chronic
Demyelinating	GBS Suramin toxicity	Hereditary polyneuropathies CIDP Lymphoma Multiple myeloma Arsenic poisoning Drugs: amiodarone, chloroquine, gold salts Diphtheria
Axonal	Alcoholism GBS variants Toxins Critical illness neuropathy Porphyria Paraneoplastic Tick paralysis	Metabolic: diabetes, hypothyroidism, chronic renal injury Drugs e.g. alcohol, vincristine, vinblastine, phenytoin, organophosphates, statins, metronidazole, dapsone Infections e.g. leprosy, HIV, borreliosis Autoimmune e.g. Sjogrens's syndrome, SLE, RA Toxins e.g. lead Vitamin deficiencies e.g. B1, B6, B12, vitamin E, folic acid Hereditary polyneuropathies Paraproteinemia: multiple myeloma (IgG), Waldenstrom's macroglobulinemia, MGUS Paraneoplastic e.g. carcinoma of lung or ovary

11.17.1.1. GUILLAIN-BARRE SYNDROME (GBS)

"It is an acute inflammatory demyelinating polyradiculoneuropathy with weakness and areflexia."

QUICK FACTS: GUILLLAIN-BARRÉSYNDROME	
Pathology:	**Upper respiratory/ gastrointestinal infection → cross-reacting antibodies to myelin → lymphocytic infiltration and demyelination**
Presentation:	**Preogressive symmetrical ascending weakness** **Hyporeflexia or areflexia** **Acroparesthesias** **Bowel and bladder sparing** **Respiratory failure**
Diagnosis:	**Clinical diagnosis** **CSF: albuminocytologic dissociation** **Nerve conduction studies, needle EMG** **PFTs: to monitor for impending respiratory failure**
Treatment:	**Plasmapharesis or IVIG**

PATHOPHYSIOLOGY:

- Upper respiratory/ gastrointestinal/ other infection → formation of antibodies which cross-react with peripheral nerve components e.g. myelin → lymphocytic infiltration and demyelination

PRESENTATION:

- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common form of GBS.
    - Acroparesthesia without sensory loss
    - There is progressive symmetrical ascending weakness of extremities (some may have a descending presentation).
    - Hyporeflexia or areflexia is present.
    - Sensory loss can be present and is variable.
    - Facial nerve palsy
    - Others: dysphagia, ophthalmoplegia, dysautonomia (sinus tachycardia, labile blood pressure, orthostatic hypotension)
    - Usually weakness reaches maximum by 2 – 4weeks.
    - Bowel and bladder are spared in 95% of cases.
    - Progression may be very rapid in few patients.
    - Patients may develop respiratory failure requiring intubation.
    - Recovery may start after 4 weeks but may take up to one year. 5% may die.
- Other variants are described in table.

INVESTIGATIONS:

- CSF:
    - Albuminocytologic dissociation in 90% patients (elevated proteins with normal cell count or mild lymphocytic pleocytosis)
- Pulmonary function testing:
    - Forced vital capacity: rapid decrease to <15 ml/ kg needs intubation
    - Negative inspiratory force:rapid decrease to <60 cm of H2O needs intubation
- Nerve conduction studies:
    - Demyelination with reduced motor conduction velocities and prolonged distal motor latencies (AIDP)
- Needle EMG:
    - Reduced motor unit recruitment
    - Evidence of axonal injury (AMAN or AMSAN)
- Spinal cord imaging: to rule out myelopathy

Table 11.25: GBS VARIANTS

GBS variants	Features
Acute motor and sensory axonal neuropathy (AMSAN)	Features of AIDP + axonal motor and sensory involvement Associated with C. jejuni infection
Acute motor axonal neuropathy (AMAN)	Features of AIDP + axonal motor involvement Rapid progression to prolonged weakness Associated with C. jejuni infection
Miller-Fischer syndrome (3 – 5% cases)	Ataxia + areflexia + ophthalmoplegia CSF protein is elevated Antibodies to glycolipid GQ1b in most patients
Bickerstaff's brain-stem encephalitis	Ataxia + ophthalmoplegia + altered level of consciousness +/- hyperreflexia CSF protein is elevated and MRI findings may be present Antibodies to glycolipid GQ1b in most patients
Paraparetic motor variant	Only legs are affected + areflexia (mimicks acute spinal cord lesion)
Pharyngeal-cervical-brachial motor variant	Ptosis + facial, pharyngeal and neck flexor weakness
Ptosis without ophthalmoplegia	Ptosis
Facial diplegia	Bilateral facial palsy
Sixth nerve palsies with diplegia	Bilateral sixth nerve palsy
Pure sensory ataxic variant or acute sensory ataxic neuropathy (ASAN)	Sensory ataxia + areflexia + absence of ophthalmoplegia
Acute sensory neuropathy	
Acute pandysautonomia	Multiple autonomic dysfunctions

MANAGEMENT:

- Definitive treatment:
    - Plasmapharesis 5 – 6 exchanges over 1 – 2 weeks
    - IVIG 0.4 g/ kg/ day for 5 days
- Steroids: not beneficial and may prolong dependency
- Radicular pain: acetaminophen, NSAIDs, gabapentin
- Physical therapy and rehabilitation

Table 11.26: DIAGNOSTIC CRITERIA OF GUILLAIN-BARRE SYNDROME		
Required	**Supportive**	**Exclusionary**
Progressive symmetric weakness of >1 limb Hyporeflexia or areflexia Progression <4 weeks Symmetric weakness	Sensory symptoms or signs Cranial nerve involvement especially bilateral facial palsy Autonomic dysfunction CSF protein elevation CSF cell count <10/mm3 Electrophysiologic features of demyelination Recovery	Other causes of excluded (toxins, botulism, porphyria, diphtheria)

⇨ ***AIDP is the most common form of Guillain-Barre syndrome.***

11.17.1.2. CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

"It is a chronic (>8 weeks) inflammatory demyelinating polyradiculoneuropathy with weakness and areflexia."

PATHOPHYSIOLOGY:
- Humoral and cell-mediated immunity against myelin and nerves

PRESENTATION:
- Progressive weakness and impaired sensory function in legs and arms

INVESTIGATIONS:
- Nerve conduction studies
- Lumbar puncture for CSF analysis: albuminocytologic dissociation

MANAGEMENT:
- Steroids e.g. PREDNISONE
- Plasmapharesis or IVIG
- Immunosuppressants e.g. AZATHIOPRINE, MYCOPHENOLATE
- Physical therapy

11.17.1.3. FRIEDRICH'S ATAXIA

"It is an autosomal recessive trinucleotide repeat disorder characterized by degeneration of many areas of nervous system mainly spinocerebellar tract, corticospinal tract and posterior columns, and peripheral nerve demyelination."

QUICK FACTS: FRIEDRICH'S ATAXIA	
Pathology:	**GAA repeats in frataxin gene region → degeneration of different parts of nervous system**
Presentation:	**Spinocerebellar tracts and cerebellum: ataxia, nystagmus, loss of fast saccadic movements** **Lateral corticospinal tracts: extensor plantar responses, loss of deep tendon reflexes, weakness** **Posterior columns: loss of vibration and position, positive Romberg's test**

	Peripheral nerve demyelination: sensory neuropathy → absent reflexes, wasting of muscles, decreased tone) **Cardiac involvement, musculoskeletal deformities**
Diagnosis:	**MRI, electrophysiology**
Treatment:	**No specific treatment**

PATHOPHYSIOLOGY:

- GAA repeats in FRDA gene region (codes for frataxin) on chromosome 9 → Degeneration of 1) spinocerebellar tract, lateral corticospinal tract and posterior columns, 2) IX, X and XII cranial nerve nuclei, 3) deep cerebellar nuclei, 4) Betz cells in precentral gyrus and 5) extensive peripheral nerve demyelination

PRESENTATION:

- It presents in children or young adults.
- Spinocerebellar tracts and cerebellum: ataxia of trunk and limbs, nystagmus, loss of fast saccadic movements, truncal titubation, dysarthria, dysmetria
- Lateral corticospinal tracts: extensor plantar responses, loss of deep tendon reflexes, weakness (distal > proximal and involved lower limbs only)
- Posterior columns: loss of vibration and position sense, positive Romberg's test
- Peripheral nerve demyelination: sensory neuropathies (absent reflexes, wasting of muscles, decreased tone)
- Cardiac involvement, musculoskeletal deformties (bilateral pes cavus, pes equinovarus, scoliosis, spina bifida), mental retardation, diabetes, optic atrophy

INVESTIGATIONS:

- MRI shows atrophy of involved areas
- Electrophysiology shows normal or mildly reduced conduction velocities in motor nerves but small or absent sensory action potentials

MANAGEMENT:

- No specific treatment
- ? role of 5-hydroxytryptophan, coenzyme Q, idebenone

⇨ ***Friedrich's ataxia is the most common inherited ataxia.***

⇨ ***It is the only trinucleotide repeat disorder with an autosomal recessive mode of inheritance.***

11.17.1.4. HEREDITARY MOTOR AND SENSORY NEUROPATHIES (HMSN)

Aka Charcot-Marie-Tooth disease (CMT)

QUICK FACTS: HEREDITARY MOTOR AND SENSORY NEUROPATHIES	
Pathology:	**Mutations in peripheral myelin and other proteins**
Presentation:	**Progressive foot, distal leg, hand and forearm weakness, diminished or absent tendon reflexes**
Diagnosis:	**Clinical diagnosis** **Nerve conduction studies**
Treatment:	**Supportive treatment**

PATHOPHYSIOLOGY:

- Mutations in peripheral myelin protein-22 (PMP22) in CMT type1

PRESENTATION:

- There is usually a family history.
- Slowly progressive distal weakness:
  - Foot and distal leg weakness →frequent trips and falls, pes cavus, hammer toe, foot drop, weak peroneal muscles
  - Hand and forearm weakness: poor finger control, difficulty buttoning and zipping, clumsiness
  - Diminished or absent tendon reflexes

- May have sensory ataxia

INVESTIGATIONS:

- Clinical examination
- Nerve conduction studies
- CBC, ESR, ANA, UCE, serum and urine electrophoresis

MANAGEMENT:

- Supportive management
- Podiatric care
- Physical and occupational therapy
- Genetic counseling

⇨ ***CMT = Inherited + progressive distal weakness + atrophy + sensory loss***

⇨ ***Hereditary motor and sensory neuropathies are the most common inherited neuropathies.***

11.17.1.5. DIABETIC NEUROPATHIES

"It is a group of neuropathies caused by long-standing diabetes mellitus."

QUICK FACTS: DIABETIC NEUROPATHIES	
Pathology:	**Prolonged diabetes → oxidative stress, polyol pathway, AGEs → damage to neurons**
Presentation:	**Distal symmetric neuropathy, small-fiber neuropathy, autonomic neuropathy, mononeuropathy**
Diagnosis:	**Clinical examination, workup of diabetes** **EMG and nerve conduction studies**
Treatment:	**Optimize glucose control, neuropathic medicines**

PATHOPHYSIOLOGY:

- Damage to neurons by oxidative stress, polyol pathway, advanced glycation end-products, etc.
- It affects 50% of patients with diabetes.

PRESENTATION:

- Distal symmetric neuropathy:
  - Most common form.
  - Affects sensory, motor and autonomic nerves but sensory abnormalities predominate.
  - Commonly present as painful paresthesias and numbness.
  - Symptoms begin in toes and ascend in stocking-type pattern. Later symptoms begin in hands and ascend in a glove-type pattern.
  - It predisposes to foot ulcers.
- Small-fiber neuropathy:
  - Affects small sensory fibers.
  - It presents as painful paresthesias and loss of distal pinprick and temperature sensations.
- Autonomic neuropathy:
  - It may present with gastrointestinal, cardiovascular and genitourinary features and sweat glands.
- Mononeuropathy:
  - It occurs from ischemia of a peripheral nerve.
  - It includes diabetic third nerve palsy.

INVESTIGATIONS:

- Clinical examination
- Tests related to diabetes
- EMG and nerve conduction studies

MANAGEMENT:

- Optimize glucose control
- Neuropathic medicines
- Diabetic foot care

11.17.1.6. LEPROSY

See 3.6.16.2. Leprosy

11.17.1.7. VITAMIN B12 DEFICIENCY

- It causes distal symmetric polyneuropathy.

PRESENTATION:

- Early disease: distal symmetric numbness, reduced proprioception and vibration sense, gait instability
- Late disease: distal weakness and muscle atrophy
- Patients may have other features of vitamin B12 deficiency e.g. SCD, anemia

INVESTIGATIONS:

- Nerve conduction studies
- Vitamin B12 levels: low
- Methylmalonic acid or homocysteine levels: raised
- Workup of vitamin B12 deficiency

MANAGEMENT:

- Vitamin B12 supplementation

11.17.2. MONONEUROPATHIES

PATHOPHYSIOLOGY:

These are usually caused by one of the following mechanisms:

- Direct trauma: tight gripping of tools,
- Compression by a local structure e.g. tumor, cast, crutches
- Prolonged pressure against bony prominences
- Entrapment syndromes caused by compression of nerves in small passages e.g. carpal tunnel syndrome

They can be demyelinating type or of axonal type in case of severe entrapment.

INVESTIGATIONS:

- Clinical examination
- Electrodiagnostic tests

MANAGEMENT:

- Treat underlying disease.
- Rest and avoid repetitive trauma
- Steroid injections
- NSAIDs or steroids for inflammation
- Relieve compression e.g. removal of tumor
- Braces or splints to prevent contractures
- Surgery for nerve entrapments

Table 11.27: CAUSES OF MONONEUROPATHIES
Cranial neuropathies e.g. oculomotor palsy caused by diabetes, facial nerve palsy (Bell palsy, Ramsay Hunt syndrome)
Median nerve compression (carpal tunnel syndrome)
Ulnar nerve compression at elbow (tardy ulnar palsy or cubital tunnel syndrome)
Radial nerve compression (crutch palsy)
Tibial nerve compression (tarsal tunnel syndrome)
Other nerves prone to injury: femoral nerve, sciatic nerve, peroneal nerve

11.17.2.1. BELL PALSY

Aka Idiopathic facial paralysis

"It is an idiopathic acute unilateral lower motor neuron type paralysis of facial nerve."

QUICK FACTS: BELL PALSY	
Pathology:	**Idiopathic or reactivation of HSV-1 → lower motor neuron type facial palsy**
Presentation:	**Lower motor neuron facial palsy**
Diagnosis:	**Clinical diagnosis, facial nerve EMG**
Treatment:	**Steroids, anti-virals** **Facial physiotherapy** **Eye care**

PATHOPHYSIOLOGY:

- Idiopathic or reactivation of herpes simplex type-1 → edema and ischemia of facial nerve → compression within facial canal

PRESENTATION:

- Usually exposure to cold before the symptoms
- Unilateral lower motor neuron type facial palsy:
  - Drooping of angle of mouth, loss of nasolabial fold, loss of wrinkling on same side of fore-head
  - Feeling of numbness or stiffness on affected side
  - Decreased lacrimation (affected side)
  - Hyperacusis (affected side)
- Complications: corneal ulceration, cosmetic problems

INVESTIGATIONS:

- Diagnosis is clinical (differentiate from upper motor neuron lesions of facial nerve)
- Facial nerve EMG

MANAGEMENT:

- General treatment:
  - Eye care:
    - Ocular lubrication with artificial tears during day and lubricating eye ointment at night)
    - Taping eye in case of corneal ulcers
    - Glasses or goggles to protect from dust
    - Eye-patch at night
- Steroids are effective: PREDNISONE 1 mg/ kg/ day for one week (an also be given as a tapering dose over)
- Anti-virals (controversial):
  - ACYCLOVIR 400 mg five times daily for 7 – 10 days
  - VALACYCLOVIR 1 g three times daily for 7 – 10 days
- Surgery:
  - Surgical decompression: controversial
  - Procedures for improving eyelid closure: tarsorrhaphy, eyelid implants, etc.

11.17.2.2. RAMSAY HUNT SYNDROME

- It is an acute lower motor neuron facial palsy caused by herpes zoster.
- Presentation: pain in ear → vesicular eruption in external auditory meatus and on mastoid region → facial palsy
- Management: PREDNISONE + ACYCLOVIR

11.17.2.3. CARPAL TUNNEL SYNDROME (CTS)

PATHOPHYSIOLOGY:

- Repeated flexion-extension at wrist or deposition of soft tissue at wrist → compression of median nerve in carpal tunnel

CAUSES:

- Repeated manual work, diabetes mellitus, pregnancy, rheumatoid arthritis, obesity, amyloidosis, acromegaly

PRESENTATION:

- Pain, paresthesias or numbness in palmar surface of first three digits
- Weakness of hand especially thumb
- Tinel sign: percussion of median nerve at carpal tunnel produces symptoms
- Phalen sign: flexing hands at 90 degrees in a prayer like position produces symptoms
- Weakness of abductor pollicis brevis
- Thenar atrophy

INVESTIGATIONS:

- EMG and NCV

MANAGEMENT:

- Wrist splinting
- Local steroid injections
- NSAIDs and diuretics: probably of no benefit
- Carpal tunnel release surgery

11.17.3. MONONEUROPATHY MULTIPLEX

"It is neuropathy involving multiple nerves in an asymmetrical fashion."

PATHOPHYSIOLOGY:

- Mononeuropathy multiplex associated with vasculitis → autoimmune attack on vasa nervorum → ischemia and infarction of nerves

PRESENTATION:

Classical disease is a medical emergency. It presents with symptoms evolving over hours to days.

- There is acute motor weakness e.g. wrist drop or foot drop.
- Soon another nerve is involved at a different asymmetrical site.
- In severe cases generalized vasculitic infarction may occur which may cause respiratory paralysis.

INVESTIGATIONS:

- Eletrophysiologic studies and needle EMG may be normal in first few weeks.

MANAGEMENT:

- High-dose corticosteroids + cyclophosphamide
- Treatment of underlying cause

Table 11.28: CAUSES OF MONONEUROPATHY MULTIPLEX		
	Acute	**Chronic**
Demyelinating	Diphtheria	Leprosy Paraproteinemia
Axonal	Diabetes Vasculitis Lyme disease Cryoglobulinemia	Diabetes Neoplastic Infiltration HIV Sarcoidosis Amyloidosis

11.18. DISORDERS OF NEUROMUSCULAR TRANSMISSION

11.18.1. MYASTHENIA GRAVIS

"It is a syndrome characterized by progressive fatiguable weakness due to poor functioning at the neuromuscular junction."

QUICK FACTS: MYASTHENIA GRAVIS	
Pathology:	**Antibodies to Ach → reduced post-synaptic response → fatigue upon repeated stimulation**
Presentation:	**Fatigueable weakness of muscles: dysarthria, dysphagia, facial weakness Ptosis**
Diagnosis:	**Tensilon test, EMG with repetitive nerve stimulation Anti-acetylcholine receptor antibodies, anti-MUSK**
Treatment:	**Acute attack: respiratory support, plasmapharesis, IVIG Long-term: anticholinesterases, immunosuppressants, thymectomy, avoid drugs which precipitate myasthenia**

PATHOPHYSIOLOGY:

- In normal persons, at the motor-end plate neuronal impulse leads to release of acetylcholine from the pre-synaptic membrane → binds to acetylcholine receptor at the post-synaptic membrane → increased conductance of sodium and potassium ions → produces end-plate potential in muscle fiber and leads to contraction. Acetylcholine is either degraded by the cholinesterase or diffuses away.
- Antibodies to acetylcholine receptor in neuromuscular junction or AchRA → reduced post-synaptic response to Ach → prone to fatigue upon repeated stimulation.

PRESENTATION:

- It is characterized by slow progression with periodic exacerbations.
- Fatiguable weakness of muscles (with intact sensation and reflexes)
    - Power good in start but diminishes gradually during exertion.
    - Weakness is worst towards the end of the day.
    - Involved muscles include:
        - Cranial muscles: extra-ocular muscles, eyelis, facial muscles, difficulty in chewing, slurred speech. These may lead to bulbar features: dysarthria, dysphagia, facial weakness, weakness of mastication, slurred speech.
        - Limb muscles: usually proximal and asymmetric and more in arms and extensors.
        - Ocular features:
            - Ptosis usually bilateral and asymmetrical
- Myasthenic crisis: respiratory failure in severe cases may require ventilator support. It is usually precipitated by aspiration or infection.
- Neonatal myasthenia: seen in children of myasthenic mothers up to 3 weeks and is identified by poor sucking and weak cry.
- Associations: thymic hyperplasia, thymoma, autoimmune diseases (e.g. SLE, RA), hypothyroidism.

INVESTIGATIONS:

- Tensilon test:
  - Principle: a short acting cholinesterase improves features of myasthenia.
  - Identify the clinical features which should be observed for improvement.
  - 1 mg EDROPHONIUM is given iv as a test dose.
  - If tolerated then 3 mg iv dose is given and observed for improvement in 30 – 60 seconds.
  - If no response then repeat 3 mg dose and observe for improvement.
  - If still there is no tesponse then a third 3 mg dose is given. If still there is no response then the test is negative.
  - If there is improvement then test is positive and patient is likely to have myasthenia gravis.
- Ice pack test:
  - A cold ice pack is applied on the eye-lid for 2 minutes.
  - Ptosis improves in myasthenia gravis.
- Electromyography with slow repetitive nerve stimulation (RNS):
  - Decremental or fatiguable response (decrease in compound muscle action potential or CMAP by 10% or more).
  - Single-fiber electromyography is more sensitive.
- Autoantibodies:
  - Anti-acetylcholine receptor antibodies (AchRA) in >80%.
    - Sub-types: binding, modulating and blocking.
  - Anti-muscle specific kinase antibodies (anti-MUSK).
  - Other antibodies .eg against titin and ryanodine receptors.
- Screen for other associated autoimmune disorders.
- Screen for thymoma using CT and MRI of chest.

MANAGEMENT:

For acute attacks:

- Intubation in respiratory failure
- Plasmapharesis: 5 exchanges on alternate days
- IV immunoglobulins 2 g/ kg daily for 5 days
- Steroids are avoided in acute state as they may worsen symptoms initially.

Pharmacological (long-term):

- Anticholinesterases:
  - PYRIDOSTIGMINE up to 600 mg per day in divivided doses.
  - NEOSTIGMINE 15 – 375 mg orally in divided doses.
- Immunosuppressants:
  - Steroids in poorly responsive (first-line immunosuppressants)
  - Azathioprine 2 – 3 mg/ kg/ day orally, in steroid-refractory disease
  - Other options are cyclosporine, cyclophosphamide or mycophenolate mofetil.
- Thymectomy: should be done in case a thymoma is found.

General:

- Beware of drugs which worsen myasthenia: D-penicillamine, interferon alpha, aminoglycosides, fluoroquinolones, calcium channel blockers, magnesium, iodinated contrasts, etc.

⇨ ***It is the most common neuromuscular junction disorder.***

11.18.2. LAMBERT-EATON MYASTHENIC SYNDROME

"It is an autoimmune paraneoplastic syndrome caused by abnormal pre-synaptic acetylcholine release."

QUICK FACTS: LAMBERT-EATON MYASTHENIC SYNDROME	
Pathology:	**Antibodies to P/ Q type voltage gate calcium channels → decreased acetylcholine release from pre-synaptic membrane**
Presentation:	**Limb weakness (usually proximal lower limbs)** **Hypoactive or absent deep tendon reflexes, autonomic dysfunction** **Associated: small cell carcinoma lung, other malignancies**
Diagnosis:	**Antibodies to P/ Q type VGCCs** **EMG with repetitive nerve stimulation, single fiber EMG**

Treatment:	**3,4-DAP, guanidine hydrochloride** **Severe cases: plasmapharesis, IVIG**

PATHOPHYSIOLOGY:

- Antibodies against P/Q-type voltage-gated calcium channels →decrease ACh release from pre-synaptic membrane → weak response (ACh release improves with repetitive stimulation).

PRESENTATION:

- Muscle weakness
  - Limbs (more pronounced):
    - Proximal muscles and lower limbs are more affected.
    - Usually have waddling gait, difficulty climbing stairs, difficulty rising from chair, etc.
  - Ocular and oculopharyngeal (less common and milder than myasthenia)
  - Respiratory muscles: usually not severe and rarely progresses to respiratory failure
- Hypoactive or absent deep tendon reflexes
- Autonomic dysfunction: dry mouth, orthostatic hypotension, constipation, impotence, pupils dilated and weakly responsive to light.
- Associations:
  - Malignancies: small cell carcinoma lung, other malignancies (lymphosarcoma, malignant thymoma, carcinomas of breast, stomach, etc.)
  - Autoimmune disorders

INVESTIGATIONS:

- Antibodies against P/Q-type voltage-gated calcium channels (P/Q-type VGCCs)
- Other antibodies:
  - Organ-specific: antibodies to thyroid, gastric parietal cells or skeletal muscle)
  - Non-organ-specific: ANA, AMA
- Electromyography with slow repetitive nerve stimulation (RNS):
  - Low CMAP, usually a decremental responseto slow RNS, marked facilitation at 20 – 50 Hz
- Single-fiber electromyography

MANAGEMENT:

- Workup for malignancy and its treatment removal of tumor may be curative. If no malignancy is found continue regular surveillance.
- 3,4-diaminopyridine (3,4-DAP):blocks voltage-gated potassium channels
- Guanidine hydrochloride:inhibits mitochondrial calcium uptake
- Anti-cholinesterases: not useful
- In severe cases: plasmapharesis, IVIG

Table 11.29: DIFFERENCES BETWEEN MYASTHENIA GRAVIS AND LAMBERT-EATON SYNDROME

	MYASTHENIA GRAVIS	LAMBERT-EATON SYNDROME
Cause	Antibodies to acetylcholine receptor	Antibodies to calcium channels
Onset	Usually start with ptosis and progress to limb weakness	Usually starts with limb weakness and progresses to ptosis
Exercise	Symptoms worsen with exercise	Symptoms improve with exercise
Association	Thymoma	Small cell carcinoma of lung
Repeated nerve stimulation tests	Decremental response	Incremental response

11.18.3. BOTULISM

See 3.6.7.2.

11.19. MYOPATHIC DISORDERS

Table 11.30: CLASSIFICATION OF MYOPATHIES	
Inflammatory	Polymyositis, dermatomyositis, inclusion body myositis, sarcoid myopathy
Systemic inflammatory diseases	SLE, RA, scleroderma, Sjögren syndrome
Infectious	HIV Viruses (e.g. polio, coxsackie, influenza,) Bacteria (e.g. streptococci, E. coli, Yersinia, Lyme disease) Parasitic (e.g. trichinosis, cysticercosis, toxoplasmosis)
Drugs	Corticosteroids, statins, fibrates, alcohol
Metabolic and endocrine	Hypokalemia, hypophosphatemia, chronic renal failure, hypothyroidism, hyperthyroidism, hyperparathyroidism, hypovitaminosis D, Cushing's syndrome Critical illness myopathy
Primary metabolic	Acid maltase deficiency, myophosphorylase deficiency, phosphofructokinase deficiency
Channelopathies	Hypokalemic periodic paralysis, hyperkalemic periodic paralysis, hypocalcemic periodic paralysis, thyrotoxic periodic paralysis
Mitochondrial	Kearns-Sayre syndrome, MELAS, MERRF
Congenital myopathies	Central core myopathy, nemaline myopathy
Muscular dystrophies	Duchenne muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy, fascioscapulohumeral dystrophy, limb-girdle dystrophy, oculopharyngeal dystrophy, Emery-Dreifuss disease

INVESTIGATIONS:

- Creatinine phosphokinase and aldolase: elevated in muscle injury
- LFTs: ALT, AST elevated but GGT not elevated
- LDH: elevated
- Electromyography (EMG):
- Muscle biopsy: confirmatory for most
- Relevant workup e.g. myositis-specific antibodies, anti-ds DNA antibodies

TREATMENT:

- Depends upon cause

11.19.1. INFLAMMATORY MYOPATHIES

See 9.8.8

11.19.2. VIRAL MYOSITIS

- These are most commonly caused by influenza or Coxsackie virus.
- **Presentation:** fever, myalgia and weakness.
- **Investigations:** Creatine kinase may be elevated.
- **Treatment:**PREDNISONE may be beneficial.

11.19.3. STEROID MYOPATHY

- Steroids are the most common cause of drug-induced myopathy.
- **Presentation:** It usually develops slowly and is characterized by proximal muscle weakness, cushingoid appearance and chronic corticosteroid intake.
- **Investigations:** EMG, creatine kinase
- **Treatment:** stopr or reduce steroids, exercise

11.19.4. CHOLESTEROL-LOWERING AGENT MYOPATHY (CLAM)

It is caused by statins, niacin, clofibrate and gemfibrozil.
Presentation: Statins in particular can present as:

- Myopathy:muscle weakness, etc.
- Myalgia: muscle pain without elevated CK
- Myositis:muscle symptoms with elevated CK
- Rhabdomyolysis:marked CK elevation (>10 times upper limit normal) + pigment-induced nephropathy
- **Investigations:** EMG, CK
- **Management:** adequate hydration, monitor in case of asymptomatic elevations of CK, discontinue in case of rhabdomyolysis or refractory myalgias

11.19.5. CRITICAL ILLNESS MYOPATHY

- It is seen in patients with prolonged illness and stays in ICU especially those with sepsis or MODS. Patietns who receive steroids, non-depolarizing neuromuscular blockers or aminoglycosides are at particular risk.
- It may be accompanied by critical illness neuropathy.
- It presents as failure to wean from ventilator or flaccid quadriparesis.

11.19.6. HYPOKALEMIC PERIODIC PARALYSIS

- It is an autosomal dominant channelopathy involving sodium and calcium channels.
- These usually present in childhood or young adults.
- There is extreme muscle weakness which develops usually after a high-glycemic meal, vigorous exercise, viral illness, etc.
- Treament is oral or intravenous potassium during attacks. Attacks are prevented by DICHLORPHENAMIDE, ACETAZOLAMIDE or potassium-sparing diuretics.

11.19.7. MUSCULAR DYSTROPHIES

"These are a group of diseases in which there is progressive degenerative changes in muscles resulting in progressive weakness."

- Weakness may start from birth or may develop later on.
- These are listed in table: classification of myopathies.

DUCHENNE MUSCULAR DYSTROPHY:

- X-linked recessive mostly
- Affects males
- Presentation:
    - At birth normal.
    - 1 – 5 years: milestones are delayed, child falls frequently.
    - Between 5 – 12 years: Gower maneuvers to stand up from the floor, difficulty climbing stairs.
    - By 7 – 12 years they lose ability to walk and become wheel-chair bound.
    - By 21 – 25 years patients most patietns die of heart and respiratoy failure.
- **Invatigations:** include ECG, CK levels, EMG.
- **Management:**
    - PREDNISONE improves muscle strength
    - Other steroids.

BECKER MUSCULAR DYSTROPHY:

- It typically affects males and is also inherited mostly as X-linked recessive.
- Diseases is similar to Duchenne muscular dystrophy but the onset is delayed (12 years) and there is longer survival.

MYOTONIC DYSTROPHY:

- It is caused by mutations in DMPK gene or CNBP leading to a trinucleotide expansion disorder.
- Presentation: progressive muscle weakness, prolonged muscle contractions and inability to relax (e.g. delayed hand relaxation), cataracts, frontal balding, diabetes, cardiac conduction defects, cardiomyopathy, hypogonadism, hypersomnia.

11.20. PRION-RELATED DISEASES

"These are neuro-degenerative disorders characterized by rapidly progressive dementia due to accumulation of prion particles in brain."

PATHOPHYSIOLOGY:

- Prion protein in brain undergoes abnormal post-translational modification → forms abnormal beta-pleated PrP^{c} or PrP^{res}→ insoluble and forms deposits and capable of self-propagating → neuronal loss, gliosis and spongiform changes

TYPES:

- Creutzfeldt-Jakob disease (CJD):
  - Rapidly progressive dementia + focal neurological changes + myoclonus + psychiatric changes
- Variant Creutzfeldt-Jakob disease (vCJD)
  - Younger onset + painful paresthesias + psychiatric symptoms + dementia
- Gerstmann-Sträussler-Scheinker syndrome
  - Familial + cerebellar ataxia + gait disturbances + dementia
- Fatal familial insomnia
  - Progressive sleep disturbance + dysautonomia + ataxia + dementia
- Kuru
  - Reported in New Guinea cannibalistic tribes + ataxia + dementia

11.20.1. CREUTZFELDT-JAKOB DISEASE (CJD)

QUICK FACTS: CREUTZFELDT-JAKOB DISEASE	
Pathology:	**Abnormal post-translation modification of prion proteins → abnormal beta-pleated sheets → self-propagation → neuronal loss, gliosis**
Presentation:	**Rapidly progressive dementia + focal neurological deficits + myoclonic jerks + psychiatric changes**
Diagnosis:	**CSF analysis, CSF 14-3-3 protein and tau protein** **EEG, MRI brain, brain biopsy**
Treatment:	**Supportive treatment**

- It can be sporadic, familial or iatrogenic.
- It occurs in 50 – 80 year of age (sporadic form) or 30 – 50 years (familial form).
- Iatrogenic disease is caused by organ transplantation containing nervous tissue.

PRESENTATION:

- Rapidly progressive dementia + focal neurological deficits + myoclonic jerks + psychiatric changes.
- Death typically occurs in one year.

INVESTIGATIONS:

- CSF: normal cytology and glucose, mildly elevated proteins, elevated CSF 14-3-3 protein and tau protein
- EEG: periodic sharp waves on non-specific background slowing
- MRI brain: hyperintense signals in cortex, caudate and putamen on diffusion-weighted images
- Brain biopsy: spongiform change (diffuse vacuolation of neuropil), astrocytic gliosis, neuronal loss, amyloid plaques.
- Genetic testing on leucoytes or tissue

TREATMENT:

- Supportive treatment
- Quinacrine: ineffective

⇨ ***Creutzfeldt-Jakob disease is the most common prion-mediated disease.***

11.21. MITOCHONDRIAL DISEASES

- These are a group of usually maternally inherited disorders caused by dysfunctional mitochondria which lead to CNS, skeletal and other manifestations.

These include:

- Kearns-Sayre syndrome: extra-ocular muscle weakness + retinitis pigmentosa + cardiac conduction blocks + ataxia
- MELAS (Mitochondrial encephalomyopathy, lactic acidosis ans stroke-like episodes)
- MERRF (Myoclonus, epilepsy and ragged-red fibres)
- Leber hereditary optic neuropathy: subacute to acute painless optic neuropathy

INVESTIGATIONS:

- Detecting mitochondrial DNA mutations in blood
- Muscle biopsy: shows ragged-red fibres

TREATMENT:

- Symptomatic only
- Nutritional supplements
- Anti-convulsants

11.22. DISORDERS OF SLEEP

Sleep disorders are classified into:

- Insomnias: inability to fall asleep or stay asleep
- Hypersomnias: excessive and inconvenient sleep
- Sleep related breathing disorders: disorders which cause breathing difficulty during sleep
- Circadian rhythm sleep-wake disorders: sleeping time is out of alignment
- Parasomnias: unwanted events or experiences during falling asleep, sleeping or waking
- Sleep movement disorders: movements before or during sleep

11.22.1. INSOMNIA

"It is complain of inadequate sleep."

It may be divided as follows:

- According to duration:
  - Transient: insomnia for one to few nights
  - Short-term: insomnia for few days up to 3 weeks
  - Chronic: insomnia for >3 weeks
- According to cause:
  - Primary: insomnia without co-existent medical or psychiatric disorder
  - Secondary: insomnia due to psychic stress, mental disorder, or another sleep disorder or psychiatric disorder.

PRESENTATION:

- Inadequate sleep
- Difficulty falling asleep
- Frequent awakenings at night
- Persistent sleepiness or fatigue

- Awakening before time

INVESTIGATIONS:
- Polysomnography: for patients who do not respond to behavioral and pharmacological treatment

MANAGEMENT:
- Behavioral measures:
  - Regular sleep timings
  - Disengage from all activities one hour before sleep and sit and read but do not use phones/ computers etc.
  - Get out of bed if not asleep in 20 – 30 minutes.
  - Seek exposure to sunlight within 2 hours of waking in morning.
  - Avoid naps during day.
- Cognitive measures:
  - Muscle relaxation techniques
  - Good visual imaging
- Pharmacological treatment:
  - Non-benzodiazepines: ZOLPIDEM, ZALEPLON, ESZOPICLONE
  - Benzodiazepines: TEMAZEPAM, CLONAZEPAM
  - Tricyclic anti-depressants: AMITRIPTYLINE
  - Melatonin

11.22.2. NARCOLEPSY

"It is excessive day-time sleepiness and appearance of REM-related sleep phenomena during wakefulness (e.g. cataplexy, hypnagogic hallucinations, sleep paralysis)."

It begins in second decade.
It occurs due to damage to hypothalamus (? Autoimmune) which leads to deficiency of hypocretin (orexin).

PRESENTATION:
- Sudden day-time sleep attacks
- Cataplexy (abrupt loss of muscle tone in limbs or face precipitated by emotional stimuli)
- Sleep paralysis at onset or termination of sleep
- Hallucinatory experiences: hypnagogic (at sleep onset) and hypnopompic (on awakening)

INVESTIGATIONS:
- Genetic testing
- Sleep studies

MANAGEMENT:
- Modafinil
- Methylphenidate
- Dextroamphetamine
- Oxybutyrate
- Sleep hygiene

11.23. HIV AND NERVOUS SYSTEM

Table 11.31: NEUROLOGICAL MANIFESTATIONS OF HIV

CD4 count >500/ µL	HIV meningitis, shingles
CD4 count 200 – 500/ µL	Distal sensory polyneuropathy, HIV-associated dementia, mononeuropathy multiplex, HIV-associated myopathy
CD4 count <200/ µL	CNS toxoplasmosis, cryptococcal meningitis, primary CNS lymphoma, progressive multi-focal leucoencephalopathy

11.23.1. CRYPTOCOCCAL MENINGITS

See 3.12.3.cryptococcosis

⇨ ***It is the most common fungal infection of brain.***

11.23.2. PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PML)

- It is a sub-acute demyelinating infection of CNS caused by reactivation of JC virus ad subsequent infection of oligodendrocytes.

PRESENTATION:
- Subacute neurologic deficits

INVESTIGATIONS:
- CSF: usually normal
- PCR amplification for JC DNA
- MRI brain
- Brain biopsy

MANAGEMENT:
- Start HAART

11.23.3. AIDS-DEMENTIA COMPLEX

- It is a diffuse sub-cortical dementia caused by HIV virus itself.

PRESENTATION:
- Behavioral changes, cognitive dysfunction, motor impairment, ataxia, poor balance, hyper-reflexia

INVESTIGATIONS:
- CT scan brain shows cortical and sub-cortical atrophy

MANAGEMENT:
- Start HAART

11.23.4. PRIMARY CNS LYMPHOMA

- It is an isolated high-grade B-cell non-Hodgkin lymphoma caused by EBV.

PRESENTATION:
- Sub-acute neurological deficits, encephalopathy, headache and seizures in the absence of fever.

INVESTIGATIONS:
- Lumbar puncture: usually contraindicated. If done shows lymphocytic pleocytosis, elevated proteins and normal glucose.
- CSF PCR for EBV
- CT or MRI brain: single ring enhancing lesion and occasionally multiple
- Biopsy

MANAGEMENT:
- Initiate HAART
- For edema: steroids, radiotherapy, methotrexate

11.23.5. CNS TOXOPLASMOSIS

- It is a recrudescence of Toxoplasma gondii within CNS due to immunosuppression.

PRESENTATION:

- Brain lesion: Headache, fever, focal neurological deficits, altered mental status, seizures, chorea, ballism
- Retinochoroiditis: eye pain, vision loss

INVESTIGATIONS:

- CD4 count
- IgG to Toxoplasma
- Lumbar puncture: usually contraindicated. CSF shows monocytic pleocytosis
- CT or MRI brain contrast: usually multiple ring-enhancing lesions (sometimes single)

MANAGEMENT:

- Inuction: Pyrimethamine, sulfadiazine and leucovorin. Alternatively clindamycin, azithromycin or atovaquone in place of sulfadiazine.
- Maintenance: pyrimethamine and sulfadiazine or clindamycin

⇨ ***It is the most common cause of focal brain mass in HIV patients***.

11.23.6. CNS TUBERCULOSIS

It can present as tuberculoma or tuberculous meningitis.

12. HEMATOLOGY

12.1. ANEMIAS

"It is a reduction in hemoglobin which interferes with tissue oxygen delivery."

These can be classified as follows:
According to cause:

- Decreased RBC production
  - Nutritional deficiency
  - Bone marrow failure
  - Decreased erythropoietin
- Increased destruction
  - Hemorrhage
  - Hemolysis

According to mean corpuscular volume (MCV):

- With reticulocytosis
  - Hemorrhage
  - Hemolysis
- Without reticulocytosis
  - Microcytic (MCV <80fL)
  - Normocytic (MCV 80 – 100 fL)
  - Macrocytic (MCV >100fL)

PRESENTATION:

- Features of low oxygen delivery to tissues: fatigue, generalized weakness, dyspnea on exertion, orthostatic light-headedness, tachycardia, tachypnea
- Features of less pigment: pallor
- Other specific features of cause of anemia

Table 12.1: ALGORITHMIC APPROACH TO ANEMIAS

Microcytic	**Normal iron profile**	**Abnormal hemoglobin electrophoresis**	Thalassemia
		Normal hemoglobin electrophoresis	Early anemia of chronic disease Sideroblastic anemia Heavy metal poisoning e.g. lead, mercury, cadmium
	Low iron profile		Iron deficiency anemia
Normocytic	**With reticulocytosis**		Hemolytic anemias Hemorrhage Recent nutritional replacement in a nutrient deficiency anemia
	Without reticulocytosis	**With pancytopenia**	Aplastic anemia MDS, Myelofibrosis, Leukemia Tuberculosis, amyloidosis, sarcoidosis Drugs (e.g. chemotherapy) Bone marrow infiltration PNH
		Without pancytopenia	Anemia of chronic disease Anemia in CKD and CLD Red cell aplasia
Macrocytic	**Megaloblastic**		B12 deficiency, Folate deficiency Orotic aciduria
	Non-megaloblastic		Liver disease, Alcoholism, Hypothyroidism, Myelodysplasia Reticulocytosis

⇨ ***Iron deficiency anemia is the most common type of anemia.***

12.2. MICROCYTIC ANEMIAS

"Anemias associated with a low mean corpuscular volume (<80 fL) are called microcytic anemias."

CAUSES:

- Iron-deficiency anemia (MOST COMMON): due to acute or chronic blood loss e.g. menstrual/ gastrointestinal bleeding
- Thalassemias
- Sideroblastic anemia
- Heavy metal poisoning e.g. lead, cadmium, mercury
- Early anemia of chronic disease

12.2.1. IRON-DEFICIENCY ANEMIA

"It is an anemia caused by deficiency of iron."

QUICK FACTS: IRON-DEFICIENCY ANEMIA	
Pathology:	**Low iron stores → less formation of hemoglobin and red blood cells**
Presentation:	**Features of anemia** **Others: pica, pagophagia, hair loss, oral ulcers, cheilosis, koilonychia, restless legs, cold intolerance, brittle nails, Plummer-Vinson syndrome**
Diagnosis:	**Microcytic anemia, increased RDW,** **Iron profile: raised TIBC, low ferritin and percentage saturation** **Bone marrow biopsy: low stainable iron**
Treatment:	**Oral iron, parenteral iron**

PRESENTATION:

- Features of anemia
- Peculiar features: pica, pagophagia (especially in children), hair loss, oral ulcers, cheilosis, koilonychia, smooth tongue, restless legs, cold intolerance, brittle nails, headaches, Plummer-Vinson syndrome

INVESTIGATIONS:

- CBC: low hemoglobin/ hematocrit, decreased number of RBCs, platelets count usually increased, low MCV and MCH
- Red cell distribution width: raised (>14) as compared to thalassemias where it is low
- Peripheral smear: microcytic, hypochromic RBCs, anisocytosis, poikilocytosis, target cells, pencil cells
- Iron profile: decreased ferritin (usually <12 ng/mL or <30 ng/mL in anemic patient), increased TIBC, low transferrin saturation (usually <15%), decreased serum iron, low hepcidin
- Bone marrow biopsy: low stainable iron by Prussian blue stain
- Workup for bleeding: e.g. pelvic ultrasound for uterine fibroids, fecal occult blood and endoscopy for GI blood loss

MANAGEMENT:

- Oral iron e.g. FERROUS SULFATE 325 mg daily on empty stomach
- Parenteral iron e.g. IRON OXIDE with polyglucose sorbitol carboxymethyl ether
- Ferric pyrophosphate citrate added to the dialysate in patients with CKD
- Blood transfusion: in severe anemia or in patients with cardiopulmonary disease

$$\boldsymbol{Iron\ deficit\ in\ mg} = (\boldsymbol{Desired\ Hb} - \boldsymbol{Patient's\ Hb}) \times \mathbf{250}$$

$$\boldsymbol{Iron\ deficit\ in\ mg} = \boldsymbol{weight\ in\ kg} \times (\boldsymbol{Desired\ Hb} - \boldsymbol{Patient's\ Hb}) \times \mathbf{2.4} + \boldsymbol{depot\ iron}$$

⇨ ***Chronic bleeding is the most common cause of iron deficiency anemia.***

Table 12.2: CAUSES OF IRON DEFICIENCY	
Chronic blood loss	Menstrual blood loss Menorrhagia due to any cause (e.g. fibroids) Gastrointestinal blood loss (e.g. peptic ulcer disease, GI malignancy, polyps, hookworm infestation) Hemoglobinuria Iron sequestration e.g. pulmonary hemosiderosis
Dietary deficiency	Vegan diet Not taking foods rich in iron
Malabsorption	Malabsorption syndromes e.g. celiac disease Zinc deficiency
Increased requirements	Children (especially if exclusively on human milk) Adolescents Pregnancy and lactation

12.2.2. THALASSEMIAS

"These are hereditary disorders characterized by deficient synthesis of globin chains (α orβ)."

12.2.2.1. β-THALASSEMIAS

QUICK FACTS: BETA-THALASSEMIA	
Pathology:	**Defect in one or both β-globin genes → deficient β-chains → excess α-chains bind together → hemolysis → hyper-proliferation of bone marrow and extra-medullary hematopoiesis**
Presentation:	**Repeated blood transfusions since 6 months of age** **Bone marrow expansion: bone tenderness, abnormal facies, pathologic fractures** **Hepatomegaly, splenomegaly, cholelithiasis** **Secondary hemochromatosis**
Diagnosis:	**Microcytic anemia with normal RDW** **Mentzer index <13** **Hemoglobin electrophoresis, free erythrocyte porphyrin**
Treatment:	**Mild disease: no treatment** **Thalassemia major: regular blood transfusions, iron chelation therapy, splenectomy, allogeneic bone marrow transplantation**

PATHOPHYSIOLOGY:

- Defect in 1 or both β-globin genes (e.g. β = fully functioning, β^0 = functionless β^+ = partially functioning) → deficient production of β-chain→ excess α-chains bind together and damage RBC membranes → intra-medullary and peripheral hemolysis → hyper-proliferation of bone marrow and extra-medullary hematopoiesis

PRESENTATION:

- Incidental finding on CBC in case of thalassemia minor or intermedia
- Repeated blood transfusions starting from age of 6 months in case of thalassemia major
- Findings of bone marrow expansion in case of thalassemia major or intermedia: bone tenderness, abnormal facial structure, pathologic bone fractures
- Findings of organomegaly due to extra-medullary hematopoiesis e.g. hepatomegaly, splenomegaly
- Cholelithiasis (bilirubin stones) due to repeated hemolysis
- Complications: secondary hemochromatosis (e.g. jaundice, pigmentation), acquisition of hepatitis B/ C or HIV infections, infections with iron-loving organisms (e.g. Yersinia, mucormycosis), need for splenectomy and post-splenectomy infections.

INVESTIGATIONS:

- CBC and peripheral film
- RDW: decreased or normal
- Reticulocyte count

- Hemoglobin electrophoresis
- Free erythrocyte porphyrin: to differentiate IDA from thalassemia trait. Raised in IDA and normal in ß-thalassemia.
- Mentzer index: ratio of MCV to RBC count. <13 suggests thalassemia trait and >13 suggests IDA.

MANAGEMENT:

- Mild thalassemias: no treatment. Avoid repeated workup for iron-deficiency
- Thalassemia major:
  - Regular blood transfusions
  - Folic acid supplementation
  - Splenectomy if blood transfusion requirements are very high
  - Iron chelation therapy in case of hemochromatosis
  - Allogeneic bone marrow transplantation is curative
- Genetic counseling and prenatal diagnosis

Table 12.3: TYPES OF ß-THALASSEMIA

	ß-thalassemia major or Cooley's anemia	ß-thalassemia intermedia	Thalassemia minor
Genetic makeup	homozygous ß- chain thalassemia i.e. $ß^0/ ß^0$	$ß^0/ ß^+$ or $ß^+/ ß^+$ both partially functioning genes or one partially functioning gene with second non-funcitoning gene	heterozygous form i.e. $ß^+/ ß$ or $ß^0/ ß$
Hematocrit	28 – 40%	17 – 33%	Falls continuously without transfusion
Peripheral film	Hypochromia, microcytosis, target cells	Hypochromia, microcytosis, basophilic stippling, target cells	Severe poikilocytosis, hypochromia, microcytosis, target cells, basophilic stippling, nucleated RBCs
Hemoglobin electrophoresis	HbF pre-dominant HbA2 variable HbA almost nil	HbF 6 – 10% HbA2 up to 10% HbA up to 30%	HbA2 4 – 8% HbF 1 – 5%
Need for transfusions	Must for survival	Occasionally in conditions of stress	Almost never

12.2.2.2. α-THALASSEMIAS

QUICK FACTS: ALPHA-THALASSEMIA	
Pathology:	**Defect in one or more α-globin genes → deficient α-chains → excess ß-chains → intra-medullary and peripheral hemolysis**
Presentation:	**α - thalassemia trait carrier, α-thalassemia trait, hemoglobin H disease, hemoglobin Bart**
Diagnosis:	**Microcytic anemia with normal RDW** **Mentzer index <13** **Hemoglobin electrophoresis, free erythrocyte porphyrin**
Treatment:	**Mild disease: no treatment** **HbH disease: folic acid, avoid medicinal iron and oxidative drugs**

PATHOPHYSIOLOGY:

- Deficienct expression of 1 or more α-globin genes on chromosome 16 → deficient production of α-chain → excess ß-chains bind together and precipitate → intra-medullary and peripheral hemolysis

PRESENTATION:

- See table

INVESTIGATIONS:

- As beta thalassemias

MANAGEMENT:

- Mild thalassemias: no treatment. Avoid repeated workup for iron-deficiency
- Hemoglobin H disease:

- Folic acid supplementation
- Avid medicinal iron and oxidative drugs e.g. sulfonamides

- Genetic counseling and prenatal diagnosis

Table 12.4: TYPES OF ALPHA-THALASSEMIAS				
	α-thalassemia trait carrier	**α-thalassemia trait**	**Hemoglobin H disease**	**Hemoglobin Bart**
Genetic makeup	1 of 4 genes deleted	2 of 4 genes deleted	3 of 4 genes deleted	All 4 genes deleted
Presentation	Asymptomatic	Asymptomatic mild anemia	Moderate to severe hemolytic anemia Splenomegaly Bone changes	Presents with fatal non-immune hydrops fetalis

12.2.3. SIDEROBLASTIC ANEMIA

"Sideroblastic anemia is a group of anemias in which bone marrow fails to incorporate iron into heme and may be characterized by presence of ringed sideroblasts in bone marrow."

QUICK FACTS: SIDEROBLASTIC ANEMIA	
Pathology:	**Iron not incorporated into protoporphyrin → impaired heme production → low reticulocyte production**
Presentation:	**Features of anemia** **Features of associated disorders** **Secondary hemochromatosis**
Diagnosis:	**CBC, reticulocyte count, RDW, iron profile** **Bone marrow biopsy** **Serum lead levels**
Treatment:	**High dose pyridoxine** **Bone marrow transplantation**

TYPES:

- Primary sideroblastic anemias:
  - Congenital: X-linked sideroblastic anemia, autosomal recessive sideroblastic anemia, mitochondrial disorders, Pearson syndrome, DIDMOAD syndrome
  - Acquired: as a myelodysplastic syndrome
- Secondary sideroblastic anemias:
  - Drugs: INH, cycloserine, chloramphenicol, linezolid, pyrazinamide
  - Toxins: lead, alcohol
  - Hematological diseases: myelofibrosis, polycythemia rubra vera, myeloma, Hodgkin's lymphoma, hemolytic anemia, leukemia, erythropoietic protoporphyria
  - Inflammatory diseases: RA, SLE
  - Nutritional: pyridoxine or copper deficiency, zinc overuse
  - Others: carcinoma, myxedema, malabsorption, prolonged hypothermia

PATHOPHYSIOLOGY:

- Iron not incorporated into protoporphyrin → impaired heme synthesis and formation of ring sideroblasts → low reticulocyte production

PRESENTATION:

- Features of anemia
- Features of associated disorders e.g. RA, SLE, lead toxicity, DIDMOAD syndrome
- Complications: secondary hemochromatosis from excessive transfusions

INVESTIGATIONS:

- CBC and peripheral film: microcytic anemia; dimorphic picture (combined microcytic with normocytic or macrocytic picture); siderocytes with Pappenheimer bodies; basophilic stippling or punctate basophilia of RBCs (lead toxicity)

- Reticulocyte count: usually low
- RDW: increased
- Iron profile: normal or high iron, ferritin and transferrin saturation
- Bone marrow examination: erythroid hyperplasia; Prussian blue staining shows abundant cytoplasmic iron and engorged perinuclear mitochondria in erythroblasts (ringed sideroblasts)
- Serum lead levels: to rule out lead toxicity
- Others: pyridoxal 5' phosphate and 4-pyridoxic acid (pyridoxine deficiency), urine porphyrin profile

MANAGEMENT:

- Remove offending agent
- Treatment of underlying causes
- Replace any deficiency
- High dose PYRIDOXINE 50 – 200 mg per day
- Administer thiamine and folic acid
- Bone marrow transplantation
- Transfusion in case of severe anemia

⇨ ***Suggestive features of sideroblastic anemia: severe microcytic anemia with raised RDW, dimorphic blood picture and absence of iron deficiency***

Table 12.5: IRON PROFILE IN DIFFERENT DISORDERS

	Iron deficiency anemia	Anemia of chronic disease	Sideroblastic anemia	Thalassemias	Hemochromatosis
Iron	Low	Low	Normal/ high	Normal/ high	High
TIBC	High	Normal/ low	Low	Normal	Normal
Ferritin	Low	Normal/ high	Normal/ high	Normal/ high	High
Transferrin saturation	Low	Normal/ slightly low	Normal/ high	Normal/ high	High
RDW	High	Normal	Increased	Normal/ high	Normal

$$\textbf{\textit{Transferrin saturation}} = \frac{\textbf{\textit{Serum iron}}}{\textbf{\textit{TIBC}}} \times \mathbf{100}$$

12.3. NORMOCYTIC ANEMIAS

12.3.1. ANEMIA OF CHRONIC DISEASE

"It is an anemia encountered in the setting of hronic diseases."

QUICK FACTS: ANEMIA OF CHRONIC DISEASE	
Pathology:	**Inflammatory cytokines → suppress erythropoiesis**
Presentation:	**Features of anemia and underlying disease**
Diagnosis:	**Iron profile: low serum iron, low TIBC, low transferrin saturation, high ferritin**
Treatment:	**Treat underlying disease** **Recombinant erythropoietin**

PATHOPHYSIOLOGY:

- Inflammatory cytokines → suppress erythropoiesis

CAUSES:

- Infections: TB, lung abscess, brucellosis
- Malignancies: lung cancer, lymphomas, breast cancer
- Inflammatory diseases: RA, SLE

PRESENTATION:

- Features of anemia
- Features of underlying disease

INVESTIGATIONS:

- CBC: low Hb, low or normal MCV
- Iron profile: low serum iron, low TIBC, low transferrin saturation, high ferritin

MANAGEMENT:

- Treat underlying disease
- No need for iron unless there is concomitant iron deficiency
- Recombinant erythropoietin titrated to maintain hemoglobin in between 10 – 12 g/dL
    - Forms: EPOEITIN ALFA 50 – 100 units/ kg iv three times weekly and DARBEPOIETIN ALFA 0.45 µg/kg once monthly
    - Indications: Hemoglobin <10 g/dL in patients with CKD, RA, IBD, hepatitis C, zidovudine therapy and myelosuppressive chemotherapy.

12.3.2. APLASTIC ANEMIA

"It is an anemia caused by replacement of bone marrow with fatty tissue."

QUICK FACTS: APLASTIC ANEMIA	
Pathology:	**Bone marrow tissue replaced by fatty tissue**
Presentation:	**Features of anemia, thrombocytopenia and leucopenia** **Absence of hepatosplenomegaly and lymphadenopathy**
Diagnosis:	**Bone marrow biopsy** **Workup for underlying cause**
Treatment:	**Supportive treatment** **Anti-thymocyte globulin + cyclosporine**

PRESENTATION:

- Features of anemia:see anemias
- Features of leucopenia: frequent infections, oral ulcers

- Features of thrombocytopenia: bruises, petechiae, bleeding from any site usually mucosal e.g. gums, urine
- Complications: transformation into leukemia

INVESTIGATIONS:

- CBC: low Hb or HCt, MCV normal or mildly raised
- Iron profile: normal
- Vitamin B12 and RBC folate: normal
- Bone marrow biopsy: hypocellular marrow with absence of progenitor cells
- Others: hemoglobin electrophoresis, peripheral blood for chromosomal breakage analysis, flow-cytometry for PNH, LFTs, renal function tests, workup viral infections, ANA, anti-ds DNA, chest x-ray, abdominal ultrasound, HLA typing

MANAGEMENT:

Supportive therapy:

- Red cell transfusion keep symptom free
- Iron chelation in patients with recurrent transfusions who have ferritin levels >1000 µg/L.
- Platelets transfusion to keep platelet count of 10 x 10^9/L. if patient has risk factors for bleeding, then keep platelet count around 20 x 10^9/L.
- Maintain good hygiene. Avoid eating undercooked foods or raw fruits and vegetables.

Specific therapy:

- Immunosuppressant drugs:
    - Anti-thymocyte globulins (ATG) + CICLOSPORIN
    - Other immunosuppressants e.g. methylprednisolone, cyclophosphamide, alemtuzumab, fludarabine
- ELTROMBOPAG in severe disease refractory to immunosuppressants
- Hematopoietic stem cell transplantation

Table 12.6: CAUSES OF APLASTIC ANEMIA

Congenital	Familial aplastic anemia, Fanconi's anemia, TAR syndrome, dyskeratosis congenita
Idiopathic	Idiopathic
Radiation	Radiation
Nutritional	Severe B12 and folate deficiency
Medications	NSAIDs, chloramphenicol, sulfonamides, gold, carbamazepine
Infections	HBV, HCV, parvovirus B19, EBV, CMV, VZV, HIV,
Chemicals	Insecticides, benzene

⇨ ***Aplastic anemia = pancytopenia + bone marrow hypoplasia + absence of organomegaly + absence of lymphadenopathy.***

12.4. MACROCYTIC ANEMIAS

12.4.1. VITAMIN B12 DEFICIENCY ANEMIA

QUICK FACTS: VITAMIN B12 DEFICIENCY ANEMIA	
Pathology:	**Vitamin B12 deficiency → cell maturation withour maturation and demyelination of posterior columns**
Presentation:	**Features of anemia** **Features of B12 deficiency: stomatitis, peripheral neuropathy, sub-acute combined degeneration of cord, dementia**
Diagnosis:	**CBC, peripheral smear** **Serum vitamin B12, serum methylmalonic acid, serum homocysteine levels, bone marrow biopsy** **Workup for cause: antibodies against intrinsic factor, Schilling test**
Treatment:	**B12 rich diet, vitamin B12 supplementation**

VITAMIN B12:

- It is required in body for conversion of homocysteine to methionine and for conversion of methylmalonyl coA to succinyl coA.
- It is acquired from diet. Pepsin releases vitamin B12 from its bound in the acidic environment of stomach. Released B12 combines with intrinsic factor in the duodenum to form a complex that is recognized in the distal ileum. Vitamin B12 is absorbed from here and binds to transcobalamin in the blood to be transported to all cells of the body.

PATHOPHYSIOLOGY:

- Deficiency causes cell maturation without division → megaloblastic changes with cell line deficiency
- Deficiency also causes demyelination of posterior columns, lateral corticospinal tracts and spinocerebellar tracts → peripheral neuropathy and sub-acute combined degeneration of cord

PRESENTATION:

- Features of anemia
- Particular features of vitamin B12 deficiency: stomatitis. glossitis, peripheral neuropathy, sub-acute combined degeneration of cord, dementia(neurological manifestations of B12 deficiency can present in the absence of anemia).

INVESTIGATIONS:

- CBC: low hemoglobin/ hematocrit, raised MCV (> 100 fL and characteristically >115 fL), leucopenia, thrombocytopenia, pancytopenia
- Peripheral smear: macrocytes, macro-ovalocytes, hypersegmented neutrophils (>5 lobes)
- Serum vitamin B12: low (usually <170 pg/mL)
- Serum methylmalonic acid: high
- Serum homocysteine levels: high
- Features of ineffective erythropoiesis: raised LDH and indirect bilirubin
- Antibodies against intrinsic factor: present in pernicious anemia
- Schilling test
    - Radio-labelled B12 is given orally followed by a 1 mg injection of vitamin B12.
    - Urine is collected for 24 hours and amount of radio-labelled B12 is measured.
    - If the absorption is normal, then ≥9% of the dose appears in urine.
    - Excretion of <5% of dose indicates inadequate vitamin B12 absorption.
    - The test is now repeated with intrinsic factor added to radio-labelled vitamin B12.
    - If absorption is still inadequate, it indicates pernicious anemia.
- Bone marrow biopsy: erythroid hyperplasia, megaloblastic changes

MANAGEMENT:

- Diet rich in vitamin B12.
- IV or SC vitamin B12 100 µg once daily for first week, then once weekly for one month, then once monthly for life. OR
- Oral methylcoblamin 1 mg once daily
- Folic acid replacement 1 mg daily if deficieny
- Red blood cell transfusions are rarely needed

MONITORING:

- Following correction, reticulocyte counts increase in one week.
- Hemoglobin is usually corrected in up to 6 weeks.
- Neurological deficits take longer time and may not even be corrected if deficiency was prolonged.

Table 12.7: CAUSES OF VITAMIN B12 DEFICIENCY ANEMIA	
Dietary deficiency	Foods low in vitamin B12, vegans
Decreased production/ absorption of intrinsic factor	Gastrectomy, gastric atrophy, pernicious anemia, use of antacids, H. pylori infection
Malabsorption	Ileal resection, malabsorption syndromes, Diphyllobothrium latum infestation, chronic pancreatitis, blind loop syndrome, drugs (metformin, colchicine, neomycin, ethanol)
Defect in transportation	Transcobalamin II deficiency

12.4.2. FOLATE DEFICIENCY ANEMIA

QUICK FACTS: FOLATE DEFICIENCY ANEMIA	
Pathology:	**Vitamin B12 deficiency → anemia**
Presentation:	**Features of anemia** **Others: diarrhea, glossitis, depression, confusion**
Diagnosis:	**RBC folate, homocysteine, methylmalonic acid**
Treatment:	**Oral folate** **Oral or parenteral folinic acid**

FOLATE:

- Folate is required for maturation of RBCs and synthesis of purines and pyrimidines. It is also important in development of fetal nervous system.
- Folate is absorbed in duodenum and upper jejunum.

PATHOPHYSIOLOGY:

- Deficiency of folate → anemia

PRESENTATION:

- Features of anemia
- Particular features: diarrhea, glossitis, depression, confusion
- Increased risk of neural tube defects in newborns

INVESTIGATIONS:

- Serum folate: varies with dietary folate
- RBC folate: true indicator of folate stores
- Homocysteine: raised
- Methylmalonic acid: normal

MANAGEMENT:

- Oral supplementation with FOLATE 400 µg to 1000 µg per day.
- In a patient with combined vitamin B12 and folate deficiency, replacement of folate earlier than B12 replacement may lead to precipitation of neurological abnormalities.
- Parenteral or oral FOLINIC ACID in patients receiving folate antagonists.
- Folate is recommended for pregnant women especially in those with risk for neural tube defects.

Table 12.8: CAUSES OF FOLATE DEFICIENCY ANEMIA	
Inadequate intake	Low folate diet, chronic alcoholism, total parenteral nutrition
Impaired absorption	Malabsorption syndromes, anti-convulsants
Inadequate utilization	Folate antagonists (metformin, methotrexate, triamterene, trimethoprim), anti-convulsants
Increased demand	Pregnancy, lactation, infancy
Increased excretion	Renal dialysis

12.5. HEMOLYTIC ANEMIAS

"These are a group of anemias characterized by decreased survival of red blood cells."

These can be intermittent or continuous or immune or non-immune mediated.

PATHOPHYSIOLOGY OF HEMOLYSIS:

- Hemolysis causes release of hemoglobin from RBCs → free hemoglobin binds with haptoglobin →excess free hemoglobin is filtered through glomeruli and is absorbed by renal tubular cells → these cells may shed and appear in urine as hemosiderin → if filtered hemoglobin exceeds reabsorptive capacity of tubular cells, free hemoglobin comes in urine.
- Hemolysis also causes hemoglobinemia and methemalbuminemia if severe.
- Degradation of hemoglobin produces indirect bilirubin (usually less than 4 mg/dL)
- Hemolysis may also raise LDH (a ubiquitous enzyme)

Table 12.9: DIFFERENCES BETWEEN INTRAVASCULAR AND EXTRAVASCULAR HEMOLYSIS		
	INTRAVASCULAR HEMOLYSIS	**EXTRAVASCULAR HEMOLYSIS**
Site of hemolysis	Hemolysis occurs in blood vessels	Hemolysis occurs in spleen by macrophages
Clinical features	Usually associated with abdominal pain, dark-colored urine, pulmonary or systemic hypertension, thrombosis and erectile dysfunction	Usually splenomegaly
Peripheral smear	Usually schistocytes	Usually spherocytes
Haptoglobin	Decreased/ absent	Mildly decreased
Urine hemosiderin	Positive	Negative
Urine hemoglobin	Positive	Negative
Urine urobilinogen	Raised	Raised
Direct antiglobulin test	Usually negative but if positive it is due to complements	Positive due to IgG
Indirect bilirubin	Highly raised	Minimally raised
Lactate dehydrogenase	Positive	Positive
Examples	Paroxysmal nocturnal hemoglobinuria, cold agglutinin disease, micro-angiopathic hemolytic anemia mechanical trauma (e.g. march hemoglobinuria, cardiac valve hemolysis, vasculitis), chemical or thermal damage (snake venom, drugs in G6PD deficiency)	Hemoglobinopathies, unstable hemoglobins, enzymopathies, membrane defects, vitamin B12 deficiency anemia, autoimmune hemolytic anemia, drug-induced

Table 12.10: TYPES OF HEMOLYTIC ANEMIAS	
INTRINSIC	**EXTRINSIC**
Membrane defects: Hereditary spherocytosis, hereditary elliptocytosis, PNH **Enzymopathies:** Pyruvate kinase deficiency, G6PD deficiency, methemoglobinemia, severe hypophosphatemia **Hemoglobinopathies:** Sickle cell anemia, thalassemia, unstable hemoglobins, methemoglobinemia	**Immune-mediated:** Auto-immune hemolytic anemia, lymphoproliferative disease, drug-induced Microangiopathic: TTP, HUS, DIC, cardiac valve hemolysis, metastatic adenocarcinoma, vasculitis, copper overload **Infections:** Plasmodium, Clostridium, Borrelia **Hypersplenism** **Burns**

12.5.1. SICKLE CELL ANEMIA

"It is an inheritedhemolytic anemia characterized by polymerization of hemoglobin and distortion of red blood cells in conditions of stress, making them prone to hemolysis and vaso-occlusion."

QUICK FACTS: SICKLE CELL ANEMIA	
Pathology:	**Mutation in ß-chain → HbS → polymerizes in conditions of stress → distortion of RBC membranes → hemolysis + vaso-occlusion**
Presentation:	**Intermittent hemolytic anemia** **Aplastic crisis** **Vaso-occlusive crises: painful bones, dactylitis, pulmonary infarction, splenic infarction, splenic sequestration, priapism** **Others: functional hyposplenia, gall stones, retinopathy, renal isosthenuria**
Diagnosis:	**CBC, peripheral smear** **Hemoglobin electrophoresis, sodium metabisulphite test**
Treatment:	**Acute care: iv hydration, opioids, oxygen, transfusion, exchange transfusion for vaso-occlusive crises** **Chronic: allogeneic hematopoietic stem cell transplantation, hydroxyurea, omega-3 fatty acids**

- It is an autosomal recessive disorder.

PATHOPHYSIOLOGY:

- Mutation causes Glu→Val substitution on position 6 of ß-chain on chromosome 11 →forms alpha-2 beta^{s}-2 (HbS) → HbS is prone to polymerization in conditions of stress e.g. acidosis, hypoxia, hypercarbia, dehydration, infection, changes in temperature → distortion of RBC membranes leads to sickle cells → cause hemolysis as well as vaso-occlusion

PRESENTATION:

Acute presentations:

- Intermittent hemolytic anemia
  - Occurs on conditions of stress.
  - Usually self-limited.
  - Causes features of hemolytic anemias e.g. anemia, jaundice, pigment gall stones.
- Aplastic crisis: it is precipitated by concomitant parvovirus B19 infection. Bone marrow suppression cannot compensate for ongoing hemolysis.
- Vaso-occlusion:
  - Bone crises: painful bones e.g. tibia, humerus, femur which are usually self-limited. Avascular necrosis of large joints may also occur e.g. hip and shoulder.
  - Hand-foot syndrome (dactylitis) and avascular necrosis of metacarpals and metatarsals.
  - Acute chest syndrome: pulmonary infarction due to sickling. It presents with chest pain, respiratory distress, pulmonary infiltrates and hypoxia.
  - Splenic infarctions: there is splenomegaly in childhood which shrinks with repeated infarctions.
  - Splenic sequestration crisis: sudden pooling of RBCs in spleen causing massive splenomegaly and hypo-volemic shock.

- Priapism
- Ophthalmologic complications: retinal infarcts, vitreous hemorrhage
- Renal papillary necrosis with hematuria
- Other featurs: cerebral sinus thrombosis, cerebral arterial infarction, mesenteric infarction, osteomyelitis (typically by Salmonella and Staphylococci), etc.

Chronic presentation:

- Pigment gall stones
- High output cardiac failure
- Pulmonary hypertension
- Functional hyposplenia (increased susceptibility to infections with encapsulated bacteria) and autosplenectomy
- Proliferative retinopathy and retinal detachment
- Renal isosthenuria and proteinuria
- Chronic leg ulcers (usually over lateral malleoli)
- Failure of growth and sexual maturation

INVESTIGATIONS:

- CBC: anemia
- Peripheral smear: sickle-shaped RBCs, reticulocytosis, nucleated RBCs, Howell-Jolly bodies, target cells
- Hemoglobin electrophoresis: HbS 85-98%, raised HbF
- Sodium metabisulphite test

MANAGEMENT:

- General measures:
  - Avoid high altitudes and conditions of hypoxia.
  - Keep well hydrated.
- Supportive care:
  - IV Hydration
  - Red blood cell transfusions if needed
  - Oxygen
  - Pain relief with opioids
  - Correct acidosis
  - Exchange transfusion in case of severe vaso-occlusive crisis, intractable pain crisis, acute chest syndrome, sustained priapism and stroke.
- Allogeneic hematopoietic stem cell transplantation is curative
- HYDROXYUREA: increases HbF thus decreases polymerization
- Omega-3 fatty acid supplementation (decreases vaso-occlusive crises rates)
- Folic acid supplementation
- Vaccines for pneumococcus, hemophilus and meningococcus
- Prenatal diagnosis for couples at risk

SICKLE CELL TRAIT:

- It is presence of heterozygous hemoglobin genotype.
- They have normal CBC and peripheral smear.
- Up to 40% of hemoglobin is HbS type.
- They are at risk for rhabdomyolysis, venous thromboembolism and sickle cell anemia related renal disease.

SICKLE-THALASSEMIA:

- It arises when one globin chain locus bears sickle cell mutation and the other bears thalassemia mutation.

- It may be sickle-β^0 thalassemia or sickle-β^+ thalassemia.
- They develop anemia, painful episodes, retinopathy, painful ulcers and repeated infections.
- Treatment is supported.

12.5.2. HEREDITARY SPHEROCYTOSIS

"It is familial hemolytic anemia in which the defects in RBC membrane lead to a loss of RBC surface area as well as predisposition to osmotic fragility."

QUICK FACTS: HEREDITARY SPHEROCYTOSIS	
Pathology:	**Defect in RBC membrane → loss of surface area → spherocyte formation → destroyed by reticulo-endothelial cells**
Presentation:	**Hemolytic anemia with intermittent jaundice, splenomegaly, pigment gall stones**
Diagnosis:	**Investigations of hemolytic anemia: low Hb, increased reticulocytes, increased LDH, increased indirect bilirubin Osmotic fragility test; Flow cytometry**
Treatment:	**Symptomatic treatment, splenectomy**

- It is an autosomal dominant disease.

PATHOPHYSIOLOGY:

- Defect in RBC membrane (deficient proteins like spectrin, ankyrin, band 3 and protein 4.2) → loss of surface area of RBCs and reduced volume → formation of spherocytes → removed by reticuloendothelial system

PRESENTATION:

Disease is usually familial.

- Hemolytic anemia with intermittent jaundice
- Splenomegaly
- Pigment gall stones

INVESTIGATIONS:

- CBC: anemia, low MCV, high MCHC
- Peripheral smear: spherocytes, increased reticulocytes
- Osmotic fragility test: spherocytesswell and rupture easily in hypotonic solutions
- Direct antiglobulin test: negative
- Flow cytometry using EMA binding test

MANAGEMENT:

- Mild disease: symptomatic treatment
- Severe disease: splenectomy

12.5.3. GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY (G6PDD)

"It is an inherited hemolytic anemia with deficient glucose-6-phosphate dehydrogenase enzyme which results in decreased ability of red blood cells to deal with oxdative stress."

QUICK FACTS: GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY	
Pathology:	**Deficiency of G6PD → decreased glutathione → oxidative stress**
Presentation:	**Episodic hemolytic anemia with intermittent jaundice (exposure to some trigger e.g. drugs, fava beans) Pigment gall stones**
Diagnosis:	**CBC and peripheral smear: hemolytic anemia, bite cells, blister cells, Heinz bodies; G6PD assay and levels**
Treatment:	**Supportive treatment; Avoid triggers**

- It is an X-linked recessive disease.

PATHOPHYSIOLOGY:

- G6PD deficiency → decreased reduced form of glutathione → increased H2O2 → denatures hemoglobin formation of Heinz body → removal by reticulo-endothelial cells

It is of two types:

Mild form:

- It is seen in African-Americans.
- Only old RBCs are deficient in G6PD.
- Hemolysis is triggered by infections or drugs.
- Hemolysis is self-limited.

Severe form:

- It is seen in Mediterranean people.
- Young as well as old RBCs are deficient in G6PD.
- Hemolysis is usually triggered by ingesting fava beans.
- Hemolysis continues until the precipitant is removed from the body. May require repeated transfusions during this time.

PRESENTATION:

- Episodic hemolytic anemia with intermittent jaundice
- Jaundice is usually precipitated by some trigger e.g. ingestion of fava beans or drugs (dapsone, methylene blue, phenzopyridine, primaquine, rasburicase, nitrofurantoin, trimethoprim-sulfamethoxazole, sulfadiazine, quinolones, quinine)
- Pigment gall stones

INVESTIGATIONS:

- Features of hemolytic anemia
- Peripheral film: bite cells or blister cells, on cresyl violet staining Heinz bodies
- G6PD assay: deficient NADPH
- G6PD levels: low (may be normal during hemolytic episode because deficient RBCs are already destroyed)

MANAGEMENT:

- Avoid triggers
- Maintain hydration
- Blood transfusions as needed

12.5.4. AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

"It is a hemolytic anemia in which there autoantibodies against RBC membrane antigens."

QUICK FACTS: AUTOIMMUNE HEMOLYTIC ANEMIA	
Pathology:	**Autoantibodies to RBC membrane → intravascular or extravascular hemolysis**
Presentation:	**Anemia + jaundice** **Splenomegaly** **Acrocyanosis, dark-colored urine, difficulty finding compatible blood** **Features of underlying disease**
Diagnosis:	**Investigations of hemolytic anemia: low Hb, increased reticulocytes, increased LDH, increased indirect bilirubin** **Spherocytes (cold) or agglutinated RBCs (warm)** **Direct Coomb's test**
Treatment:	**Warm: steroids, plasmapharesis, splenectomy, immunosuppressants** **Cold: avoid cold exposure, rituximab, immunosuppressants**

PATHOPHYSIOLOGY:

- Autoantibodies bind with RBC membrane antigens → intravascular or extravascular hemolysis or extravascular destruction

PRESENTATION:
- Features of anemia + jaundice + features of underlying disease
- Splenomegaly (in warm AIHA)
- Mottling or numbness of digits, acrocyanosis, low-back pain, dark colored urine (in cold AIHA)
- Difficulty finding compatible blood for transfusion

INVESTIGATIONS:
- CBC: anemia (if concomitant thrombocytopenia then it is called Evans syndrome)
- Peripheral smear: spherocytes in warm AIHA, agglutinated RBCs in cold AIHA
- Direct Coomb's test

MANAGEMENT:
- Warm AIHA:
  - Steroids e.g. PREDNISONE 1 – 2 mg/ kg/ day
  - Plasmapharesis in case of severe hemolysis
  - Splenectomy in non-responders
  - If still does not respond then immunosuppressants e.g. RITUXIMAB, AZATHIOPRINE, CYCLOPHOSPHAMIDE. Another option is DANAZOL.
  - RBC transfusions if severe anemia
  - Folate supplements
  - Treat underlying disorder
- Cold AIHA:
  - Avoid exposure to cold
  - No role of steroids or splenectomy
  - RITUXIMAB is first-line treatment.
  - Other immunosuppressants e.g. CYCLOPHOSPHAMIDE
  - RBC transfusions if severe anemia

Table 12.11: TYPES OF AUTOIMMUNE HEMOLYTIC ANEMIAS

	WARM AIHA	COLD AIHA OR COLD AGGLUTININ DISEASE
Types of antibodies	IgG	IgM
Binding temperature	Bind to RBC membranes at 37ºC	Bind to RBC membranes at 0ºC - 5ºC
Hemolysis type	Extravascular	Intravascular and in cold parts of body
Direct Coomb's test	RBCs coated with IgG	RBCs coated with complement
Site of sequestration	Mainly spleen and also liver	Liver
Examples	Lymphomas and leukemias e.g. CLL Connective tissue diseases e.g. SLE Drugs e.g. methyldopa	Idiopathic Malignancies e.g. lymphoma, CLL Waldenström's macroglobulinemia Infections e.g. Mycoplasma pneumonia, infectious mononucleosis, CMV, measles, mumps

12.5.5. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

"It is an acquired clonal hematopoietic disorder characterized by abnormal sensitivity of red blood cells to complement-mediated lysis."

QUICK FACTS: PAROXYSMAL NOCTURNAL HEMOGLOBINURIA	
Pathology:	**PIGA mutations → deficient GPI → RBCs prone to complement-mediated damage → depletes NO → vasoconstriction**
Presentation:	**Dark urine at night, hemolytic anemia** **Large vessel thromboses (venous and arterial)** **Deficient hematopoiesis** **Features of NO deficiency e.g. esophageal spasms, erectile dysfunction, abdominal pain**
Diagnosis:	**Flow cytometry of RBCs and WBCs**

	Bone marrow biopsy
Treatment:	**Mild: no treatment** **Severe: allogeneic stem-cell transplantation, eculizumab**

PATHOPHYSIOLOGY:

- Mutations in PIGA gene → deficient glycosyl-phosphatidylinositol (GPI) → lack of binding of GPI-linked proteins to blood cells (decay accelerating factor CD55, homologous restriction factor, C8 binding protein, membrane inhibitor of reactive lysis or CD59) →increased complement-mediated lysis → depletes nitric oxide → smooth muscle contraction with consequent vasoconstriction
- Hemolysis also leads to hemoglobinuria

PRESENTATION:

- Dark urine at night
- Intravascular hemolytic anemia
- Large vessel thromboses (venous and arterial) e.g. mesenteric vein thromboses, Budd-Chiari syndrome, cerebral vein thrombosis, splenic vein thrombosis, dermal vein thrombosis
- Deficient hematopoiesis
- Features of NO deficiency: esophageal spasms, erectile dysfunction, abdominal pain, back pain, fatigue, pulmonary hypertension
- Renal failure
- Complications: AML, iron-deficiency

INVESTIGATIONS:

- CBC: anemia, pancytopenia
- Peripheral smear: macro-ovalocytes, polychromasia
- Urine hemosiderin: positive
- Iron profile: iron deficiency
- Flow cytometry of RBCs and WBCs: deficient CD55 and CD59
- Bone marrow: hypoplasia or erythroid hyperplasia or both

MANAGEMENT:

- Mild disease: no treatment
- Severe disease:
    - Allogeneic hematopoietic stem cell transplantation in possible candidates
    - ECULIZUMAB monoclonal antibody against C5 to reduce hemolysis and thrombosis
- Iron replacement
- Corticosteroids reduce hemolysis

⇨ ***PNH = hemolytic anemia + pancytopenia + thrombotic events***

12.6. LYMPHOMAS AND LEUKEMIAS

12.6.1. HODGKIN'S LYMPHOMA (HL)

"It is a type of lymphoma characterized by malignant clonal proliferation of Reed-Sternberg (RS) giant cellsin a normal reactive cellular background."

QUICK FACTS: HODGKIN'S LYMPHOMA	
Pathology:	**Decreased apoptosis → survival of post-germinal center B cells → RS cells**
Presentation:	**Lymphadenopathy** **Splenomegaly, hepatomegaly, extra-nodal involvement** **B symptoms (fever, weight loss, night sweats)**
Diagnosis:	**Lymph node biopsy** **Workup for staging**
Treatment:	**Induction: ABVD, BEACOPPescalated, MOPP, Stanford V** **Initial: chemotherapy, radiotherapy**

- It usually occurs in young adults around 20 – 30 years of age or in middle-aged (>50 years) of age.

PATHOPHYSIOLOGY:

- Post-germinal center B cells survive apoptosis due to some trigger (e.g. EBV infection) which deranges NFkappaB pathway →RS cells enlarged and secrete chemokines → Th2 response causes a surrounding inflammatory infiltrate while at the time same time escaping recognition

TYPES:

- Nodular sclerosing (MOST COMMON TYPE)
- Mixed cellularity
- Lymphocyte depleted (LEAST COMMON WITH WORST PROGNOSIS)
- Lymphocyte rich
- Nodular lymphocyte predominant

PRESENTATION:

- Lymphadenopathy
  - Usually painless and progressive
  - Usual location: supra-clavicular, cervical, axillary, mediastinal
  - Characteristically pain occurs on drinking alcohol in some.
- Splenomegaly, hepatomegaly
- Extranodal involvement: (more common in intermediate- or high-grade lymphomas)
  - GI tract, skin, bone marrow, sinuses, genitourinary tract, testes, CNS.
- Systemic symptoms (B symptoms): (more common in intermediate- or high-grade lymphomas)
  - These include fever, weight loss (>10% from baseline within 6 months) and night sweats.
- Bone marrow involvement:
  - Features of pancytopenia
- Others:
  - Fatigue, weakness, pruritis, cough, cranial nerve palsies

INVESTIGATIONS:

- CBC, ESR
- Blood chemistry including CRP, LDH, alkaline phosphatase, liver enzymes, albumin.
- Screen for hepatitis B and C, and HIV
- Lymph node biopsy is diagnostic: presence of typical or atypical RS cells in a background of reactive granulocytes, lymphocytes, macrophages, plasma cells, fibroblasts.
- Staging: PET/ CT scan whole body
- Bone marrow biopsy

MANAGEMENT:

- Induction therapy:
  - ABVD: DOXORUBICIN/ BLEOMYCIN/ VINBLASTINE/DACARBAZINE)
  - BEACOPPescalated: BLEOMYCIN, ETOPOSIDE, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINCRISTINE, PROCARBAZINE, PREDNISONE
  - MOPP: MECHLORETHAMINE, VINCRISTINE, PROCARBAZINE, PREDNISONE)
  - Stanford V: DOXORUBICIN, VINBLASTINE, MUSTARD, BLEOMYCIN, VINCRISTINE, ETOPOSIDE, PREDNISONE + radiotherapy
- Initial therapy:
  - Stage I or II: short course chemotherapy + radiotherapy or full course chemotherapy
  - Stage II with large mass or III or IV: full course ABVD
- Salvage therapy: it is employed when initial therapy fails
  - ICE, DHAP and ESHAP regimes
- Relapsed disease:
  - High dose chemotherapy followed by autologous stem cell transplantation
  - BRENTUXIMAB VEDOTIN + AVD
  - Immune checkpoint inhibitors: NIVOLUMAB, PEMBROLIZUMAB

PROGNOSIS:

- 10-year survival:
  - >90% for stage I or II
  - 50 – 60% for stage III or IV

Table 12.12: ANN-ARBOR STAGING OF HODGKIN LYMPHOMA	
I	Single lymph node area or a single extra-nodal site
II	Two or more lymph node areas on the same side of diaphragm
III	Lymph node areas on both sides of diaphragm
IV	Disseminated or multiple involvement of extra-nodal areas

12.6.2. NON-HODGKIN'S LYMPHOMA (nHL)

"It is a type of lymphoma characterized by malignant clonal proliferation of B cells, T cells and NK cells without presence of Reed-Sternberg cells."

QUICK FACTS: NON-HODGKIN'S LYMPHOMA	
Pathology:	**Over-expression of oncogene → lymphoma**
Presentation:	**Lymphadenopathy** **Pancytopenia** **B symptoms** **Extra-nodal involvement** **Complications: DIC, effusions, spinal cord compression, bowel obstruction, SVC syndrome**
Diagnosis:	**Lymph node biopsy** **Workup for staging** **Lumbar puncture (high-grade)**
Treatment:	**Radiotherapy, chemotherapy, autologous stem cell transplantation, intra-thecal chemotherapy**

TYPES ACCORDING TO CELL OF ORIGIN:

- B-cell (85%)
- T-cell and NK –cell (15%)

PATHOPHYSIOLOGY:

- An oncogene is juxtaposed next to an immunoglobulin gene (B-cell lymphoma) or T-cell receptor gene (T-cell lymphoma) → over-expression of oncogene → development of lymphoma

PRESENTATION:

- Lymphadenopathy
  - Isolated or multiple
- Features of bone marrow involvement e.g. pancytopenia
- Systemic symptoms (B symptoms):
  - These include fever, weight loss (>10% from baseline within 6 months) and night sweats.
- Extranodal involvement: (more common in intermediate- or high-grade lymphomas)
  - GI tract, skin, bone marrow, liver.
- Complications:
  - Pancytopenia, DIC, infections, pleural and pericardial effusions, spinal cord compression, bowel obstruction, SVC syndrome, etc.

INVESTIGATIONS:

- Lymph node biopsy for diagnosis
- PET/ CT scan whole body for staging
- Bone marrow biopsy
- Lumbar puncture (in high-grade lymphomas)

MANAGEMENT:

- Indolent lymphomas:
  - Localized radiotherapy
  - RITUXIMAB + BENDAMUSTINE
  - R-CVP (RITUXIMAB, CYCLOPHOSPHAMIDE, VINCRISTINE, PREDNISONE) or
  - R-CHOP (RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, PREDNISONE)
- Aggressive lymphomas:
  - Diffuse large B-cell lymphoma: R-CHOP. Involved nodal radiotherapy (INRT) for bulky disease.
  - Mantle cell lymphoma: chemotherapy + autologous hematopoietic stem cell transplantation
  - Primary CNS lymphoma: high dose METHOTREXATE + RITUXIMAB
  - Burkitt lymphoma or lymphoblastic lymphoma: intense chemotherapy like ALL + intrathecal chemotherapy
  - Peripheral T-cell lymphoma: autologous stem cell transplantation, BRENTUXIMAB VEDOTIN

⇨ ***Presence of 1) RS cells and 2) reactive inflammatory infiltrate distinguishes Hodgkin's lymhphoma from non-Hodgkin's lymphoma.***

12.6.3. ACUTE LEUKEMIAS

"These are malignancies of circulating white blood cells with an aute presentation."

QUICK FACTS: ACUTE LEUKEMIAS	
Pathology:	**Clonal malignancies of lymphoid or myeloid precursors**
Presentation:	**Acute presentation** **Frequent infections, bleeding tendencies, hepatomegaly, splenomegaly, lymphadenopathy** **Features of leukostasis**
Diagnosis:	**CBC with peripheral film** **Flow cytometry and immunohistochemistry** **Bone marrow biopsy**
Treatment:	**Chemotherapy**

ACUTE LYMPHOBLASTIC LEUKEMIA:

- It is a clonal malignancy of lymphoid precursor cells with resultant proliferation of immature lymphoid cells. It may be of B-cell type, T-cell type or both. Favorable prognosis is suggested by hyperdiploidy and t(12;21). Hypodiploidy, Philadelphia chromosome i.e. t(9;22), t(4;11) and multiple chromosomal abnormalities are associated with a poor prognosis.

ACUTE MYELOID LEUKEMIA:

- It is a clonal malignancy of myeloid precursor cells with resultant proliferation of immature myeloid cells.
- Favorable cytogenetics include t(8;21), inv (16)(p13;q22). Unfavorable cutogenetics include monosomy 5 or 7, presence of two or more other monosomies, presence of three or more cytgenetic abnormalities.

ACUTE PROMYELOCYTIC LEUKEMIA:

- It is characterized by t(15;17) which leads to fusion gene PML-RAR-α. It is treated using All-trans-retinoic acid (ATRA) and arsenic oxide (ATO). It has a very good prognosis.

PRESENTATION:

Patients usually have an acute presentation of few days.

- Due to immature leucocytes: frequent infections especially bacterial and fungal infections.
- Due to thrombocytopenia: bleeding tendencies, bruises
- Organ invasion: organomegaly e.g. hepatomegaly, splenomegaly.
- Due to hyperleucostasis (WBC>100,000/ μL): chest pain, stroke, headache, blurred vision.
- Due to meningeal invasion: headache, nausea, seizures, papilledema, cranial nerve palsies
- Due to cytokines: anorexia, weight loss, fever
- Due to organ infiltration: meningeal leukemia, testicular mass.
- Metabolic abnormalities: hyponatremia, hypokalemia, increased LDH, hyperuricemia, rarely lactic acidosis

INVESTIGATIONS:

- CBC: usually shows pancytopenia with circulating blasts.
    - Blasts are absent from peripheral smear in case of “aleukemic leukemia”.
    - Auer rods are pathognomonic of AML.
- Uric acid: high
- Bone marrow biopsy: hypercellular picture dominated by blasts (>20%).
- Flow cytometry and immunohistochemistry:
    - AML: CD13, CD33 or myeloperoxidase
    - ALL: terminal deoxynucleotidyl transferase (TdT)
        - B-cell type:
            - CD19 and mostly CD10
        - T-cell type:
            - Absence of mature T-cell markers (CD3, 4 or 8) and absence of surface immunoglobulins.
            - Presence of CD2, 5 and 7.
- Others:
    - Chest x-ray may show mediastinal mass.
    - CSF may show blasts in case of meningeal leukemia.

MANAGEMENT:

- General measures:
    - Avoid crowded places because of risk of infections.
    - Food and personal hygiene.
    - Supportive therapy: blood transfusions and colony stimulating factors for cytopenias, treatment of toxic effects of chemotherapy.
- AML:
    - Induction therapy usually involves an anthracycline (doxorubicin or idarubicin or danurubicin) or anthracenenedione (mitoxantrone) + cytarabine.
    - Consolidation involves stem cell transplantation or cytarabine chemotherapy in young patients. Conservative treatment of other chemotherapy is used in elderly.
- ALL:
    - Chemotherapy involves induction, consolidation and maintenance regimes.

- The regimes typically involve cyclophosphamide, an anthracycline (doxorubicin or idarubicin or danurubicin), glucocorticoids (prednisone or dexamethasone), vincristine and L-asparaginase e.g. hyper-CVAD regime (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone).
- Rituximab is added in case of CD20+ B-cell ALL.
- Tyrosine kinases (e.g. imatinib, nilotinib, ponatinib) are added in case of Philadelphia chromosome positivity.
- CNS prophylaxis is also given because of high risk of meningeal leukemia.
- Patients over age 60 years have a poor prognosis.

- APML:
  - ATRA or ATO.

Table 12.13: COMPARISON OF CLASSIFICATION OF ACUTE MYELOGENOUS LEUKEMIAS	
WHO CLASSIFICATION OF LEUKEMIAS	**FRENCH-AMERICAN-BRITISH CLASSIFICATION OF LEUKEMIAS**
AML with recurrent genetic abnormalities	**M0:** Minimally differentiated leukemia
AML with myelodysplasia-related changes	**M1:** Myeloblastic leukemia without maturation
Therapy related myeloid neoplasms	**M2:** Myeloblastic leukemia with maturation
AML not otherwise specified	**M3:** Hypergranular promyelocytic leukemia
Myeloid sarcoma	**M4:** Myelomonocytic leukemia
Myeloid proliferations related to Down syndrome	**M5:** Monocytic leukemia
Blastic plasmacytoid dendritic cell neoplasm	**M6:** Erythroleukemia (DiGuglielmo's disease)
Acute leukemia of ambiguous lineage	**M7:** Megakaryoblastic leukemia

⇨ ***Acute lymphoblastic leukemia is the most common leukemia in children.***
⇨ ***Acute myeloid leukemia is the most common acute leukemia in adults.***

12.6.4. CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

"It is a chronic leukemia which is characterized by excessive proliferation of mature lymphocytes which are functionally defective."

QUICK FACTS: CHRONIC LYMPHOCYTIC LEUKEMIA	
Pathology:	**Monoclonal proliferation of lymphocytes → loss of ability to differentiate into plasma cells**
Presentation:	**Asymptomatic, frequent infections, glandular swellings, Pallor, bruising, lymphadenopathy, splenomegaly, hepatomegaly**
Diagnosis:	**CBC, peripheral smear Flow cytometry Bone marrow biopsy Immunophenotyping**
Treatment:	**Chemotherapy Allogeneic bone marrow transplantation**

- It usually occurs in elderly persons (>60 years).

PATHOPHYSIOLOGY:

- Unknown factors → monoclonal proliferation of mature lymphocytes → loss of ability to differentiate into antibody-forming plasma cells

PRESENTATION:

It has indolent and slowly progressive course.

- Usually asymptomatic (incidentally discovered on CBC)
- Immunosuppression: Frequent respiratory, skin and mucosal infections
- Organ infiltration: painless generalized lymphadenopathy, splenomegaly, hepatomegaly
- Bone marrow failure: anemia, thrombocytopenia
- Autoimmune hemolytic anemia or autoimmune thrombocytopenia
- Others: fatigue, weight loss, skin rashes, easy bruising, bone tenderness, abdominal pain

INVESTIGATIONS:

- CBC: lymphocytosis usually 50 x 10^9/ L, anemia, thrombocytopenia, neutropenia
- Peripheral smear: small lymphocytosis, smudge cells (fragile lymphocytes which break while making slide)
- Flow cytometry: clonal B cell population
- Bone marrow biopsy: infiltrating leukemic cells
- Immunophenotyping: co-expression of CD19 and CD5, expression of CD23, low surface expression of IgG and CD20, absence of translocation or over-expression of cyclin D1.

MANAGEMENT:

Chemotherapy

- <70 years:
  - FCR (FLUDARABINE, CYCLOPHSOPHAMIDE, RITUXIMAB) or
  - BR (BENDAMUSTINE, RITUXIMAB) or
  - IBRUTINIB
- ≥70 years
  - CHLORAMBUCIL or
  - CHLORAMBUCIL + OBINUTUZUMAB
- Refractory/ relapsed disease:
  - IBRUTINIB, IDELALISIB + RITUXIMAB
- Allogeneic bone marrow transplantation

PROGNOSIS:

- Stage I – II: normal life expectancy
- Stage III – IV: >90% 2-year survival

Table 12.14: RAI CLASSIFICATION OF CHRONIC LYMPHOCYTIC LEUKEMIA

Stages	Features	Risk
0	Lymphocytosis only	Low
I	Lymphocytosis + lymphadenopathy	Low
II	Organomegaly	Intermediate
III	Anemia	High
IV	Thrombocytopenia	High

⇨ ***It is the most common leukemia in elderly.***

⇨ ***It is the leukemia with longest patient survival.***

12.6.5. CHRONIC MYELOID LEUKEMIA (CML)

"It is a chronic leukemia characterized by clonal proliferation of myeloid stem cells with loss of apacity to differentiate."

QUICK FACTS: CHRONIC MYELOID LEUKEMIA	
Pathology:	**Translocation (9,22) → continuously active phosphorylated tyrosine kinase → myeloid cell proliferation**
Presentation:	**Asymptomatic, fatigue, fever, night sweats** **Features of anemia, splenomegaly, leucostasis**
Diagnosis:	**CBC, peripheral smear, LAP score** **Bone marrow biopsy**
Treatment:	**Tyrosine kinase inhibitors** **Older agents: interferon, hydroxyurea, busulfan** **Allogeneic bone marrow transplantation**

- It usually occurs in middle-aged patients.

PATHOPHYSIOLOGY:

- Translocation t (9,22) → fusion of BCR gene on chromosome 22 with ABL1 gene on chromosome 9 → fusion gene forms a phosphorylated tyrosine kinase which is continuously active → proliferation of myeloid cells
- As a result of translocation, chromosome 22 gets smaller in size and is called Philadelphia chromosome.

PRESENTATION:

The disease has three phases:

- Chronic phase: present in >90% of patients and is usually asymptomatic.
- Accelerated phase:increasing hematological manifestations with 15 – 30% blasts.
- Blast phase:there are >30% blasts and extramedullay hematopoiesis also occurs.

It presents as:

- Asymptomatic (incidentally discovered on CBC in 40 – 50%)
- Symptoms due to hypermetabolic state: fatigue, low-grade fever, night-sweats
- Features of splenomegaly (characteristically massive): abdominal fullness, early satiety
- Features of leukocytosis/ leucostasis: blurring of vision, respiratory distress, confusion, priapism, thrombosis
- Features of anemia
- Thrombocytosis or thrombocytopenia
- Sometimes hepatomegaly

INVESTIGATIONS:

- CBC: marked leukocytosis (50 – 200 x 10^9/ L), eosinophilia, basophilia, may have anemia or thrombocytosis
- Peripheral smear: increased metamyelocytes, myelocytes, bands
- Leucocyte alkaline phosphatase (LAP)activity/ score: decreased (as compared to leukemoid reaction in which it is increased)
- Cytogenetics: in blood or bone marrow show Philadelphia chromosome
- Bone marrow biopsy:
    - Expansion of myeloid lineage, prominent megakaryocytes, mild fibrosis

MANAGEMENT:

Specific therapy:

- Tyrosine kinase inhibitors
    - First generation: IMATINIB 400 – 600 mg per day
    - Second generation: DASATINIB, NILOTINIB, SUNITINIB, BOSUTINIB
    - Third generation: PONATINIB

- Protein translocation inhibitors: OMACETAXINE
- Older options:
    - INTERFERON ALPHA
    - HYDROXYUREA
    - BUSULFAN
- Allogeneic bone marrow transplantation is curative in selected patients.
- Splenectomy or splenic irradiation if hypersplenism severe
- Leukopharesis in case of leucostatic crises
- Blast crisis has a poor response to treatment.

General measures:

- Transfusions as needed
- Care of splenomegaly

12.7. MYELOPROLIFERATIVE DISORDERS

"These are a group of disorders of clonal proliferation of myeloid cells associated with JAK2 kinase mutations."

These include:

a. Polycythemia vera
b. Myelofibrosis
c. Essential thrombocytosis
d. Chronic myeloid leukemia

12.7.1. POLYCYTHEMIA VERA

"Polycythemia vera is clonal proliferation of red blood cell precursors resulting in increased red cell mass and features of hyperviscosity."

QUICK FACTS: POLYCYTHEMIA VERA	
Pathology:	**Clonal proliferation of RBC precursors**
Presentation:	**Features of hyperviscosity or thromboses** **Occasionally bleeding episodes or features of increased histamine** **Splenomegaly, hepatomegaly, plethora, hypertension**
Diagnosis:	**CBC: increased Hb or HCt, may have increased TLC or platelets** **LAP score: raised** **Erythropoietin: low** **Bone marrow biopsy** **JAK-2 mutations**
Treatment:	**Phlebotomy, cytoreductive therapy, thromboprophylaxis** **Treatment of hyperuricemia**

PRESENTATION:

Symptoms:

- Features of hyperviscosity: headache, dizziness, vertigo, tinnitus, visual disturbances, angina pectoris, intermittent claudication
- Features of thromobosis: myocardial infarction, stroke, peripheral gangrene, mesenteric angina, hepatic vein occlusion (Budd-Chiari syndrome).
- Occasionally bleeding episodes: epistaxis, gum-bleed, ecchymoses, gastrointestinal bleeding,
- Occasionally features of increased histamine: pruritis (worsens on taking a warm bath), peptic ulcer
- Features of splenomegaly: early satiety, weight loss

Signs:

- Splenomegaly, hepatomegaly, facial plethora, hypertension.

INVESTIGATIONS:

- Rule out secondary polycythemia
- CBC: increased hemoglobin, hematocrit and red blood cells, also increased white blood cells and platelets
- Leucocyte alkaline phosphatase: raised
- Serum erythropoietin: reduced
- Vitamin B12 levels: reduced
- Uric acid: raised
- Bone marrow biopsy: hyper-cellular with all three cell lines increased
- JAK2 mutation: present

Table 12.15: WHO 2016 REVISED DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA
Diagnosis requires **All three major criteria** **OR** **First two major criteria along with minor criterion**
MAJOR CRITERIA: • Increased red cell mass indicated by: Hemoglobin >16.5 g/dl in males (or hematocrit >49%) and >16.5 mg/dl in females (or hematocrit >48%) or red cell mass >25% above predicted value • Hypercellular bone marrow (panmyelosis) • JAK2617V F or functionally similar mutation
MINOR CRITERIA: • Low erythropoietin level

MANAGEMENT:

- Phlebotomy (up to 250 – 500 ml QAD) to keep hematocrit below 45%
- Thromboprophylaxis:
  - ASPIRIN 81 mg OD PO
- Cytoreductive agents:
  - HYDROXYUREA
  - RUXOLITINIB (Janus kinase inhibitor)
  - INTERFERON ALFA-2a and ALFA-2b
  - BUSULFAN
  - ANAGRELIDE
  - Radioactive phosphorus-32 therapy
- Treatment of hyperuricemia: ALLOPURINOL 100-300 mg/ day

⇨ ***Gaisbock syndrome = hypertension + pseudopolycythemia. It is differentiated from polycythemia vera by a low red cell mass.***

⇨ ***Secondary polycythemia is differentiated from polycythemia vera by high erythropoietin level in the former.***

12.7.2. ESSENTIAL THROMBOCYTHEMIA

"It is a myeloproliferative disorder characterized by sustained megakaryocytic proliferation leading to an increased number of circulating platelets."

QUICK FACTS: ESSENTIAL THROMBOCYTHEMIA	
Pathology:	**Excessive stimulation of megakaryocyte precursors → increased platelets**
Presentation:	**Thrombotic events** **Sometimes mucosal bleeding** **Eryhtromelalgia, splenomegaly, pseudohyperkalemia**
Diagnosis:	**CBC: platelets >600 x 10E9/L (hypogranular abnormally shaped)** **Absent BCR/ ABL gene** **Bone marrow biopsy**
Treatment:	**Low dose aspirin** **Hydroxyurea, anagrelide, PEG-interferon alfa-2**

PATHOPHYSIOLOGY:

- Excessive stimulation of megakaryocyte precursors → increased circulating platelets

PRESENTATION:
- Usually thrombosis e.g. stroke, mesenteric, hepatic or portal thromboses
- Sometimes mucosal bleeding
- Erythromelalgia: painful burning of hands with erythema
- Splenomegaly
- Pseudohyperkalemia

Diagnosis requires exclusion of other causes of thrombocytosis e.g. reactive thrombocytosis (infections, bleeding) and other myeloproliferative disorders (polycythemia vera, CML).

Investigations:
- CBC: platelets >600 x 10^9/L
- Normal red cell mass
- Bcr/abl gene: absent
- Peripheral smear: hypogranular abnormally shaped platelets
- Bone marrow biopsy: increased megakaryocytes

MANAGEMENT:
- Low dose aspirin
- Specific treatment:
  - HYDROXYUREA
  - ANAGRELIDE
  - PEG-INTERFERON alpha-2

12.7.3. MYELODYSPLASTIC SYNDROMES (MDS)

"It is an acquired clonal disorder characterized by dysmyelopoiesis in bone marrow."

QUICK FACTS: MYELODYSPLASTIC SYNDROME	
Pathology:	**Clonal disorder of dysmyelopoiesis**
Presentation:	**Asymptomatic** **Macroytic anemia without megaloblasts, mild thrombocytopenia, neutropenia**
Diagnosis:	**CBC: 1 – 3 cell lines decreased, normocytic or macrocytic anemia, bilobed/ hypersegmented neutrophils** **Bone marrow biopsy** **Cytogenetics**
Treatment:	**Supportive treatment** **Erythropoietin, G-CSF**

- It is commonly found in elderly patients.

CAUSES AND PATHOPHYSIOLOGY:
- Idiopathic
- Exposure to radiation, immunosuppressants, viral infections, chemicals (e.g. benzene) →cytogenetic abnormalities/ molecular mutations/ abnormal maturation and differentiation → 1, 2 or 3 cell lines disturbed

PRESENTATION:
- Initially asymptomatic
- Marocytic anemia without megaloblasts → features of anemia
- Mild thrombocytopenia
- Neutropenia: bacterial/ fungal infections
- Splenomegaly (in CMML)

INVESTIGATIONS:

- CBC: 1 – 3 cell lines decreased
- Peripheral film: normocytic or macrocytic anemia, bilobed/ hypersegmented neutrophils
- Bone marrow biopsy: hypercellular with trilineage dysplastic changes
- Cytogenetics

MANAGEMENT:

Management is supportive.

- RBC and platelet transfusions.
- Bone marrow stimulation: erythropoietin, Granulocyte colony-stimulating factor
- Vitamin supplementation: B6, B12 and folate.
- Treat infections.
- Cytotoxic chemotherapy in those with excess blasts or AML: CYTARABINE + anthracyclines

Table 12.16: TYPES OF MYELODYSPLASTIC SYNDROMES
FAB CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES
• Refractory anemia (RA) • Refractory anemia with ringed sideroblasts (RARS) • Refractory anemia with excess blasts (RAEB) • Refractory anemia in transition to AML (RAEB-T) • Chronic myelomonocytic leukemia (CMML)
WHO CLASSIFICATION OF MYELODYSPLASTIC SYNDROMES
• MDS with single-lineage dysplasia • MDS with multi-lineage dysplasia • MDS with ring sideroblasts • MDS with isolated del (5q) • MDS with excess blasts • Unclassifiable MDS

⇨ ***Myelodysplastic syndromes = dysplastic peripheral blood + trilineage bone marrow dysplasia + hypercellular marrow + absence of vitamin deficiency***

12.8. PLASMA CELL DISORDERS

12.8.1. MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

"It is a clonal pre-malignant proliferation of plasma cells which is relatively asymptomatic."

QUICK FACTS: PLASMA CELL MYELOMA	
Pathology:	**Clonal pre-malignant proliferation of plasma cells**
Presentation:	**Asymptomatic; Absence of lytic lesions, renal involvement or hypercalcemia**
Diagnosis:	**IgG spike <3 g/ dL** **Bone marrow biopsy <10% plasma cells, Bence-Jones proteinuria <1 g/ 24 hours**
Treatment:	**Observation**

- It is a pre-malignant condition and may develop into multiple myeloma or Waldenstrom's macroglobulinemia.

PRESENTATION:

- Asymptomatic and discovered incidentally

INVESTIGATIONS:

- Diagnosis requires absence of lytic lesions, renal involvement, anemia and hypercalcemia.
- IgG spike <3 g/dL
- Bone marrow biopsy: <10% plasma cells
- Bence-Jones proteinuria: <1g/ 24 hours

TREATMENT:

- Does not require treatment. Needs close observation.

12.8.2. PLASMA CELL MYELOMA

Aka Multiple myeloma

"It is a clonal neoplastic proliferation of plasma cells which leads to overproduction of monoclonal para-proteins (M-proteins) and systemic manifestations."

QUICK FACTS: PLASMA CELL MYELOMA	
Pathology:	**Clonal proliferation of plasma cells → monoclonal para-proteins**
Presentation:	**Asymptomatic** **Bone pains (typically backache in elderly), features of anemia, thrombocytopenia, proteinuria and renal failure, hypercalcemia**
Diagnosis:	**IgG or sometimes IgM protein spikes on electrophoresis or increased free light chains** **Lytic areas on x-rays** **Bone marrow biopsy ≥10% plasma cells (≥60% for active myeloma)** **Bence-Jones proteins**
Treatment:	**Autologous hematopoietic stem cell transplantation** **Chemotherapy with alkylating agents**

PATHOPHYSIOLOGY:

1. Production of osteoclast activating factor → bone resorption
2. Bone marrow invasion by plasma cells
3. Renal failure occurs because of immunoglobulin deposition in kidneys (myeloma nephrosis) or hypercalcemia
4. Hyper-viscosity (uncommon)

PRESENTATION:

- Asymptomatic (found incidentally)
- Myeloma bone disease: bone pain (e.g. chronic back-ache in elderly, pain in ribs or jaw), pathologic fractures, spinal cord compression, loss of height.
- Myeloma bone marrow suppression: frequent infections, bleeding manifestations, fatigue.
- Myeloma kidney disease: proteinuria, renal failure

COMPLICATIONS:

- Pathological fractures
- Amyloidosis

INVESTIGATIONS:

- Serum and urine protein electrophoresis: demonstrates M-protein spikes (usually IgG, sometimes IgM)
- Serum free light chain assay
- Plain x-rays: demonstrate osteoporosis or punched-out lytic lesions particularly in spine, skull, etc.
- Bone marrow biopsy: ≥10% plasma cells
- Hyper-calcemia
- Increased total proteins and globulins
- Bence-Jones proteins in urine: (presence of light chains)
- Serum beta-2 microglobulins: high (shows bad prognosis)
- Serum albumin: low (shows bad prognosis)
- CBC: Rouleaux formation of RBCs, low TLC, low platelets, low hemoglobin.
- ESR: usually increased
- Creatinine: increased

TREATMENT:

- Treatment of choice: Autologous hematopoietic cell transplantation (HCT)

- For patients who are not candidates of HCT: Chemotherapy with alkylating agents. Examples include thalidomide alone, thalidomide ± steroids, thalidomide + melphalan, lenalidomide + dexamethasone, bortezomib + melphalan, VAD (vincristine, Adriamycin, dexamethasone), melphalan + prednisone
- For severe pain and chemotherapy unresponsive patients

PROGNOSIS:

- 5-year survival: 10 %

⇨ ***It Is characterized by presence of CRAB manifestaitons:***
C = Calcium increased, R = Renal failure, A = Anemia, B = Bone lesions
⇨ ***Most common cause of death in multiple myeloma is infections (pulmonary or urinary).***

12.8.3. WALDENSTRÖM'S MACROGLOBULINEMIA

"It is a malignant proliferation of plasmacytoid lymphocytes characterized by elevated monoclonal macroglobulins (IgM), hyper-viscosity and bone marrow infiltration."

QUICK FACTS: WALDENSTRÖM'S MACROGLOBULINEMIA	
Pathology:	**Malignant proliferation of plasmacytoid lymphocytes → increased IgM, hyperviscosity and bone marrow infiltration**
Presentation:	**Marrow infiltration, organ infiltration with features of hyperviscosity and weight loss**
Diagnosis:	**Elevated IgM, Bence-Jones proteins** **Flow cytometry, Bone marrow biopsy**
Treatment:	**Rituximab or ibrutinib, autologous stem cell transplantation in few**

- It is a type of B-cell lymphoma also known as lymphoplasmacytic lymphoma.
- MGUS is recognized as its precursor lesion.

PRESENTATION:

1. Marrow infiltration: pallor, purpura, bleeding manifestations, fatigue
2. Organ infiltration: lymphadenopathy, hepato-splenomegaly
3. Hyperviscosity: engorged retinal veins
4. General: weight loss

COMPLICATIONS:

- Hyperviscosity syndrome
- Amyloidosis
- Peripheral neuropathy

INVESTIGATIONS:

- CBC: anemia, thrombocytopenia, neutropenia
- ESR: elevated
- Elevated IgM >5 g/dL
- Bence-Jones proteinuria
- Bone marrow aspiration and biopsy
- Flow cytometry studies

TREATMENT:

- Chemotherapy: Rituximab, Ibrutinib (in case of rituximab resistance)
- In hyperviscosity presentation: plasmapharesis
- Autologous stem cell transplantation in few cases

PROGNOSIS:

- No definite cure

12.9. THROMBOCYTOPENIAS

Table 12.17: ALGORITHMIC APPROACH TO THROMBOCYTOPENIA		
Decreased production	**Nutritional deficiency**	B12 deficiency Folate deficiency
	Congenital	Alport's syndrome Fanconi's syndrome
	Marrow injury	Aplastic anemia Chemotherapy Radiation-induced Drug-induced Malignant infiltration Myelodysplasia
Sequestration	**Hypersplenism**	Chronic liver disease Malignancy Myelofibrosis
Increased destruction	**Immune-mediated**	Idiopathic thrombocytopenic purpura HIV infection Systemic diseases e.g. SLE Alloimmune Heparin-induced thrombocytopenia Drug-induced
	Non-immune	DIC HUS TTP Pre-eclampsia HELLP APS
Hemodilution		Massive transfusion Cardiopulmonary bypass

12.9.1. IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

Aka primary immune thrombocytopenia or autoimmune thrombocytopenia

"It is an isolated thrombocytopenia with normal bone marrow in the absence of other causes."

QUICK FACTS: IDIOPATHIC THRMOBOCYTOPENIA PURPURA	
Pathology:	**IgG against platelet membrane glycoproteins → phagocytosis by macrophages**
Presentation:	**Asymptomatic or features of thrombocytopenia** **Absence of splenomegaly**
Diagnosis:	**Diagnosis of exclusion** **CBC: thrombocytopenia with normal morphology** **Bone marrow biopsy**
Treatment:	**Steroids → IVIG or RhIG → rituximab → splenectomy → thrombopoieting receptor agonists** **Supportive treatment**

PATHOPHYSIOLOGY:

- IgG against platelet membrane glycoproteins → coat and damage platelets → phagocytosis by macrophages

PRESENTATION:

- Asymptomatic
- Features of thrombocytopenia: easy bruising, petechiae, purpura, bleeding tendency especially mucosal bleeding.
- Absence of splenomegaly
- Complications: intra-cranial hemorrhage

INVESTIGATIONS:

- CBC: thrombocytopenia, usually anemia is absent
- Peripheral film: normal morphology of platelets
- Ultrasound to rule out splenomegaly
- Bone marrow: normal to increased megakaryocytes

MANAGEMENT:

Acute ITP:

- First-line: oral PREDNISONE, IV METHYLPREDNISOLONE, DEXAMETHASONE
- Second-line:
  - IV immunoglobulins (IVIG) or
  - IV Rho immunoglobulins (RhIG) – given in Rh(D)positive patients with intact spleens.
- Third-line: RITUXIMAB
- Supportive therapy: platelet transfusion to control significant bleeding
- Splenectomy: if platelets fail to improve in 6 months
- Thrombopoietin receptor agonists in thrombocytopenia refractory to splenectomy: ELTROMBOPAG, ROMIPLOSTIM

PSEUDOTHROMBOCYTOPENIA:

- Pseudothrombocytopenia is the thrombocytopenia which occurs in patients having anti-EDTA antibodies. When blood is collected in EDTA bottle, platelets clump together, resulting in a falsely low platelet count.

12.9.2. THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

"It is a disease in which abnormally large von Willebrand proteins lead to small vessel thrombosis and depletion of platelets."

QUICK FACTS: THROMBOTIC THRMOBOCYTOPENIC PURPURA	
Pathology:	**Lack of ADAMTS13 → abnormally large vWF → platelet aggregation → depletion of platelets**
Presentation:	**Microangiopathic hemolytic anemia with thrombocytopenic purpura** **Other: fever, neurological features, renal failure**
Diagnosis:	**Demonstrate schistocytes, low haptoglobin, increased reticulocytes with negative Coomb's test; ADAMTS13 activity <5%**
Treatment:	**Total plasma exchange plus pulse dose steroids** **Refractory: crysupernatant, steroids, rituximab** **Do not transfuse platelets** **Aspirin or LMWH if platelets >50,000/ mm3**

- It is a medical emergency.

PATHOPHYSIOLOGY:

- Lack of a vWF cleaving protease (aka ADAMTS13 = A Disintegrin like And Metalloprotease with Thrombospondin type 1 motif 13) → abnormally large vWF multimers → platelet aggregation in micro-vessels especially in brain, heart and kidneys → depletion of platelets

FORMS:

- Congenital: inherited deficiency of ADAMTS13
- Acquired: autoantibodies against ADAMTS13
- It is associated with HIV infection, pregnancy, malignancies, pancreatitis and certain drugs (e.g. ticlopidine, cyclosporine).

CLASSIC PENTAD OF TTP: (20 – 30%)

- Microangiopathic hemolytic anemia (MAHA): anemia, shistocytes (fragmented RBCs), reticulocytosis, raised LDH levels and indirect hyperbilirubinemia.
- Thrombocytopenic purpura: petechiae, purpura, bruises, epistaxis, gingival bleeding, bleeding from other sites. Bleeding is rare.

- Fever
- Neurologic features: altered mentation, encephalopathy, coma, headache, seizures, paresis, visual disturbances, aphasia, dysarthria, paresthesias, transient ischemic attacks.
- Renal failure: proteinuria, microhematuria, azotemia

Other findings may include: pallor, jaundice, fatigue, arthralgia, myalgia, chest pain, heart failure.

DIAGNOSIS:

- Diagnosis is considered in all cases of thrombocytopenia with MAHA.
- Do CBC, UCE, PT, APTT, INR,
- MAHA is demonstrated by anemia along with schistocytes, low haptoglobin and raised reticulocyte count.
- Direct Coomb's test is negative.
- PT, APTT, INR, fibrin degradation products are all normal which differentiate it from DIC.
- ADAMTS13 activity is <5% in the absence of antibodies.

MANAGEMENT:

- Mortality is 90% if left untreated.
- Screen for HIV, HBV, HCV, autoantibodies and pregnancy.
- Total plasma exchange (PEX) using FFPs preferrably within 4 – 8 hours.
- Start pulse dose steroids with PEX: Inj METHYLPREDNISOLONE 1 g IV OD for 3 days.
- Refractory cases: cryosupernatant, steroids, RITUXIMAB.
- If platelet count is >50,000/ mm3, then start aspirin or low molecular weight heparin to prevent thrombosis.

Table 12.18: HUS VERSUS TTP

Hemolytic Uremic Syndrome	Thrombotic Thrombocytopenic Purpura
It is more common in children.	It is more common in adults.
There is usually history of diarrhea before illness.	There is usually no history of diarrhea.
Renal failure tends to be more severe.	Renal failure tends to be mild.
Neurologic features are not seen in HUS.	Neurologic features are a classic presentation.
Treatment is supportive and may include dialysis.	Treatment is total plasma exchange using fresh frozen plasma.

12.9.3. HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

"Heparin-induced thrombocytopenia is a condition in which there is antibody formation to a complex of the platelet-specific protein platelet factor 4 (PF4) and heparin."

QUICK FACTS: HEPARIN-INDUCED PURPURA	
Pathology:	**Antibody against complex between PF4 and heparin → hypercoagulability**
Presentation:	**Thrombocytopenia after receiving heparin** **Venous thrombosis but rarely bleeding**
Diagnosis:	**CBC: thrombocytopenia** **Antibodies against heparin/ PF4 assay, HIPA or SRA**
Treatment:	**Discontinue heparin** **Anticoagulate with direct thrombin inhibitors** **Avoid platelet transfusions**

PRESENTATION:

- Decrease in platelet count after receiving heparin (Should be suspected by >50% drop in platelet counts)
- Rarely bleeding; usualy thrombosis (usually venous) e.g. DVT, PE, myocardial infarction

INVESTIGATIONS:

- CBC: thrombocytopenia
- Antibodies against heparin/ platelet factor 4 (PF4) assay
- Heparin-induced platelet aggregation assay (HIPA)
- Serotonin release assay (SRA)

MANAGEMENT:

- Discontinue all heparin sources
- Start anticoagulation with alternative anti-coagulants like direct thrombin inhibitors (argatroban, lepirudin, bivalirudin, fondaparinux, danaparoid). Switch to warfarin after adequate anti-coagulation and resolution of thrombocytopenia.
- These antibodies can cross-react with low-molecular weight heparin, which should not be used for anticoagulation.
- In HIT without thrombosis, continue anticoagulation for one month.
- In HIT with thrombosis, continue anticoagulation for 3 – 6 months.
- Avoid platelet transfusion in HIT

Table 12.19: COMPARISON OF BOTH TYPES OF HEPARIN-INDUCED THROMBOCYTOPENIA		
	HIT 1	**HIT 2** **Aka HITT or heparin-induced thrombocytopenic thrombocytosis**
Pathophysiology	Non-immune	Immune-mediated
Presentation	Usually asymptomatic	Usually thrombotic episode which can be life-threatening
Timing of onset	Usually within 2 days of starting heparin	Usually 4 – 10 days after heparin therapy.
Severity	Mild	Usuallu moderate to severe
Resolution	Platelets normalize even if heparin is continued	Platelets do not normalize without stopping heparin

⇨ ***4 T's of HIT: thrombocytopenia, thrombosis, timing of thrombocytopenia and thrombocytopenia with no other explanation.***

⇨ ***Warfarin should not be introduced alone or else it may precipitate thrombosis or gangrene due to low protein C and S.***

12.10. DISORDERS OF COAGULATION

12.10.1. VON WILLEBRAND'S DISEASE (vWD)

"It is an inherited disorder caused by qualitative or quantitative deficiency of von Willebrand's disease."

QUICK FACTS: VON-WILLEBRAND DISEASE	
Pathology:	**Quantitiative or qualitative deficiency in vWF → decreased platelet aggregation and adhesion → bleeding tendency**
Presentation:	**Cutaneous and mucosal bleeding**
Diagnosis:	**BT, APTT prolonged** **Plasma vWF level and factor VIII activity: decreased** **RIPA: reduced**
Treatment:	**Mild to moderate bleeding: desmopressin** **Severe or unresponsive bleeding: factor VIII concentrates**

PATHOPHYSIOLOGY:

- Quantitative or qualitative deficiency in von Willebrand factor (vWF)→ decreased platelet aggregation and adhesion, decreased carriage of factor VIII → bleeding tendency

PRESENTATION:

- Cutaneous and mucosal bleeding:
    - Epistaxis and hematomas: MOST COMMON

- Others: easy bruising, bleeding from small wounds, gum bleeding, menorrhagia, gastrointestinal bleeding
- Complications:
  - Shock, joint deformities, acquisition of HBV, HCV or HIV from unchecked blood

INVESTIGATIONS:

- Diagnosis involves combination of clinical and laboratory findings.
- Bleeding time: prolonged
- APTT: prolonged
- Plasma vWF: decreased
- Factor VIII activity: decreased
- Ristocetin-induced platelet aggregation: reduced

MANAGEMENT:

- Desmopressin (DDAVP) is the first choice for mild – moderate bleeding (type 1 and few cases of type 2). It releases stored vWD from the endothelial cells and platelets.
- Factor VIII concentrates (contain high amounts of vWF): for major trauma, surgery, bleeding in type 3 and bleeding in type 2 which is unresponsive.
- Patients should avoid aspirin, NSAIDs and intra-muscular injections.

Table 12.20: TYPES OF VON WILLEBRAND'S DISEASE

	TYPE 1	TYPE 2	TYPE 3
Frequency	Most common IN 60 – 80%	In 15 – 30%	In 5 – 10%
Type of deficiency	Partial quantitative deficiency	Qualitative deficiency	Quantitative deficiency
Severity	Usually mild	Mild to moderate Further divided into four sub-types 2A, 2B, 2M and 2N	Severe

⇨ ***Von Willebrand disease is the most common inherited bleeding disorder.***

12.10.2. HEMOPHILIA A

"It is an inherited X-linked recessive disorder caused by qualitative or quantitative deficiency of factor VIII which leads to a bleeding tendency."

QUICK FACTS: HEMOPHILIA A	
Pathology:	**Qualitative or quantitative deficiency of factor VIII → bleeding tendency**
Presentation:	**Recurrent hemarthrosis → ankylosis** **Easy brusing and bleeding**
Diagnosis:	**PT, BT: normal** **APTT: prolonged** **Factor VIII: low** **vWF: normal** **Test for inhibitors**
Treatment:	**Factor VIII conentrates, desmopressin, FFPs, cryoprecipitate or tranexamic acid for bleeding**

EPIDEMIOLOGY:

- Primarily affects males.

PRESENTATION:

- Recurrent hemarthrosis and subsequent ankylosis (USUAL PRESENTATION IN CHILDREN)
- Easy bruising, petechial, purpura
- Bleeding tendency (significant bleeding after minor wounds/ injuries/ surgeries or even spontaneously)

- Intramuscular hematomas, retroperitoneal hematomas, hematuria, epistaxis, hemoptysis, hematemesis, melena, intra-cranial bleeding, hematospermia)
- Features of hemorrhage and shock

INVESTIGATIONS:

- Complete blood picture: normal or low hemoglobin (due to bleeding)
- Prothrombin time: normal
- Activated partial thromboplastin time: prolonged
- Bleeding time: normal
- Factor VIII level: low.
  - >10% indicates subclinical disease.
  - 5 – 10% indicates mild disease.
  - 1 – 5% indicates moderate disease.
  - <1% indicates severe disease.
- Von Willebrand factor: normal
- Testing for inhibitors: done when bleeding is difficult to control despite factor replacement
  - It is identified by patient's plasma with normal plasma.
  - If APTT becomes normal, no inhibitors are present.
  - If APTT fails to normalize, inhibitors are present.
- Screen for HIV, HBV and HCV

MANAGEMENT:

- Achieve hemostasis
  - Factor VIII concentrate for acute bleeding.
    - Maintain levels around 30% in minor bleeds, around 50% in major bleedsand 80 – 100% in life-threatening bleeds.
  - DESMOPRESSIN 0.3 µg/kg intravenously for mild to moderate hemophilia.
  - Fresh frozen plasma and cryoprecipitate should be avoided (chances of transmission of viral infection).
  - Epsilon AMINOCAPROIC ACID or TRANEXAMIC ACID in case of oral mucosal hemorrhages.
- Replace blood losses
- For patients with inhibitors of factor VIII: high-dose factor VIII, activated prothrombin complex, activated recombinant factor VIII, monoclonal antibodies e.g. EMICIZUMAB, de-sensitization
- Prevention of bleeding:
  - Transfusion of factor VIII before surgery/ dental procedure.
  - DESMOPRESSIN (DDAVP) can be given before procedures in mild disease.
  - Epsilon AMINOCAPROIC ACID or TRANEXAMIC ACID
- Gene therapy

⇨ ***Knee joint is the most common joint to be involved by hemarthrosis in hemophilia.***

⇨ ***AIDS is the most common cause of death in patients with hemophilia (due to repeated blood transfusions).***

12.10.3. HEMOPHILIA B

Aka Christmas disease

"It is an inherited X-linked recessive disorder caused by deficiency of factor IX which leads to a bleeding tendency."

QUICK FACTS: HEMOPHILIA B	
Pathology:	**Qualitative or quantitative deficiency of factor IX → bleeding tendency**
Presentation:	**Recurrent hemarthrosis → ankylosis** **Easy brusing and bleeding**
Diagnosis:	**PT, BT: normal** **APTT: normal or prolonged** **Factor VIII and vWF: normal** **Factor IX levels: low**
Treatment:	**Factor IX conentrates**

PRESENTATION:

- Similar to hemophilia A

INVESTIGATIONS:

- Complete blood picture: normal or low hemoglobin (due to bleeding)
- Prothrombin time: normal
- Activated partial thromboplastin time: normal or prolonged
- Bleeding time: normal
- Factor VIII level: normal
- Von Willebrand factor: normal
- Factor IX level: low

MANAGEMENT:

- Factor IX concentrates
- DDAVP has no role

12.10.4. DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

"It is an abnormal systemic activation of the coagulation pathways which causes generation of intravascular fibrin clots leading to multi-organ failure while at the same time causing bleeding due to depletion of platelets and coagulation factors."

QUICK FACTS: DISSEMINATED INTRAVASCULAR COAGULATION	
Pathology:	**Intravascular coagulation with loss of localization → consumption coagulopathy**
Presentation:	**Bleeding with features of underlying condition and organ dysfunction**
Diagnosis:	**Platelets: low** **PT, APTT: raised** **Fibrinogen: low** **D-dimers and FDP: raised**
Treatment:	**Treat underlying cause and give organ supportive treatment** **Avoif platelets and FFPs unless life-threatening bleeding**

PATHOPHYSIOLOGY:

- Exposure of blood to procoagulants e.g. tissue factor → intravascular coagulation with loss of localization → thrombin generation → depressed anti-thrombin III, protein C, and plasminogen activator inhibhitor → consumptive coagulopathy causes depletion of clotting factors → hemorrhage

CAUSES:

- Sepsis, burns, malignancy (e.g. AML), drug toxicity, obstetric problems (e.g. abruption placenta, amniotic fluid embolism), trauma, severe transfusion reaction, organ failure (pancreatitis, severe hepatic failure)

PRESENTATION:

- Features of underlying condition
- Bleeding e.g. gum-bleed,hematemesis
- Organ dysfunction e.g. renal failure, hepatic dysfunction, respiratory dysfunction, CNS dysfunction

INVESTIGATIONS:

- CBC: low platelets
- PT and APTT: prolonged
- Fibrinogen: low
- D-dimers and fibrin degradation products: raised

MANAGEMENT:

- Treat underlying condition e.g. sepsis
- Organ support e.g. non-invasive ventilation in respiratory failure, hemodialysis in renal failure
- Avoid platelets and/or FFPs unless there is life-threatening bleeding/ planned procedure
- Heparin in case of significant thrombosis without hemorrhage

12.10.5. VITAMIN K DEFICIENCY

- Vitamin K is a cofactor in the des-gamma carboxylation of clotting factors II, VII, IX, X, protein C and protein S. This modification is needed to bind calcium to these factors. Deficiency leads to bleeding tendency. Warfarin antagonizes the vitamin K dependent des-gamma carboxylation and also leads to coagulopathy. Since, protein C and S have short half lives, therefore sometimes a transient hypercoagulable state may occur in initial 2 – 3 days of warfarin therapy.

CAUSES:

- Use of broad-spectrum antibiotics (depletion of vitamin K synthesizing bacteria in normal flora)
- Total parenteral nutrition without vitamin K
- Malabsorption syndromes
- Warfarin therapy

PRESENTATION:

- Easy bruising
- Bleeding tendency especially mucosal bleeding

INVESTIGATIONS:

- PT: prolonged initially
- APTT: prolonged later

MANAGEMENT:

- In case of severe bleeding: fresh frozen plasma
- If not bleeding: replace vitamin K oral, SC or IV

12.10.6. LIVER DISEASE

- Liver synthesizes all the clotting factors except von Willebrand factor (which is synthesized by endothelium, subendothelial tissue and megakaryocytes).
- It is bad prognostic factor for liver disease or acute liver failure.
- It presents as bleeding tendency or overt bleeding e.g. GI bleeding.
- Investigations reveal prolonged PT initially and later prolonged APTT.
- Treatment is supportive e.g. FFPs, vitamin K, cryoprecipitate transfusion, platelet transfusion (for thrombocytopenia.

12.10.7. INHERITED HYPER-COAGULABLE STATES

CAUSES:

- Anti-thrombin III deficiency
- Antiphospholipid antibody syndrome
- Protein C deficiency
- Protein S deficiency
- Factor V Leiden mutation (or activated protein C resistance)
- Prothrombin gene mutation
- Hyperhomocysteinemia

PRESENTATION:

- Venous or arterial thromboembolic events: single or repeated usually DVT, PE. Others include mesenteric infarction, portal vein thrombosis, cerebral sinus thrombosis, etc.
- An inherited cause is suspected in case of:

- Family history of DVT, PE or thrombotic events
- Recurrent episodes of DVT, PE or thrombotic events
- Age <40 years at first event
- Thrombosis at unsual sites e.g. mesenteric veins, renal veins, cerebral veins, etc.

INVESTIGATIONS:

- Functional assays

MANAGEMENT:

- Anti-coagulation for 3 – 6 months
- Life-long anticoagulation if two or more thromboembolic events

12.11. ANTI-COAGULATION

ANTI-COAGULANT DRUGS:

Anti-coagulants are divided into following classes:

- **Oral coumarin derivatives:** warfarin, dicumarol
- **Indirect anti-thrombin III inhibitors:** heparin, enoxaparin, dalteparin, nadroparin, danaparoid
- **Direct thrombin inhibitors:** hirudin, bivalirudin, argatroban, lepirudin, desirudin
- **Oral direct thrombin inhibitors:** dabigatran
- **Factor Xa inhibitors:** fondaparinux
- **Oral factor Xa inhibitors:** apixaban, rivaroxaban, edoxaban

FIBRINOLYTIC/ THROMBOLYTIC DRUGS:

- Streptokinase, urokinase
- Tissue plasminogen activator (t-PA): alteplase, reteplase, tenectelase
- Anistreplase

ANTI-THROMBOTIC/ ANTI-PLATELET DRUGS:

- **Irreversible COX inhibitors:** aspirin, triflusal
- **Adenosine reuptake inhibitors:** dipyrimadole
- **Phosphodiesterase inhibitors:** cilostazol
- **ADP receptor inhibitors:** ticlopidine, clopidogrel, prasugrel, ticagrelor
- **GPIIB/ IIIA inhibitors:** abciximab, eptifibatide, tirofiban
- **Protease-activated receptor-1 (PAR-1) antagonists:** vorapaxar
- **Thromboxane inhibitors:** terutroban

13. TOXICOLOGY

13.1. TOXICOLOGY

It is the branch of science concerned with the nature, effects, detection and management of poisons.

13.2. TOXIDROMES

It is a constellation of symptoms and signs produced by a specifc group of posions.

Table 13.1: FEATURES OF DIFFERENT TOXIDROMES

Toxidrome	Conscious level	Respiratory function	Vitals	Pupils	Sweating	Othes
Cholinergic toxidrome	None	No direct effect Bronchorrhea may cause respiratory failure	HR ↓ or sometimes ↑ BP ↓ Temperature Φ	Miosis (may be pin-point)	Increased	Bowel and bladder activity increased Fasciculations +
Anti-cholinergic toxidrome	Agitatation, withdrawal	No direct effect	HR ↑ BP ↑ Temperature ↑	Mydriasis	Decreased	Bowel and bladder activity decreased
Sympatho-mimetic toxidrome	Agitation, delirium	No direct effect	HR ↑ BP ↑ Temperature ↑ RR ↑	Mydriasis	Increased	Bowel and bladder activity normal or increased
Sedative-hypnotic toxidrome	Sedation, coma	Depressed	HR ↓ BP ↓ HR ↓ Temperature ↓	No change	Decreased	Bowel and bladder activity may be decreased
Opioid toxidrome	Sedation, coma	Depressed	HR ↓ BP ↓ HR ↓ Temperature ↓	Constricted (may be pinpoint)	Decreased	Bowel and bladder activity may be decreased
Serotonin syndrome	Confusion, agitation, coma	Normal	HR ↑ BP ↑ Temperature ↑ RR ↑	Ocular clonus Mydriasis	Increased	Bowel and bladder activity may be increased Hyper-reflexia Tremors Autonomic instability
Neuro-leptic malignant syndrome	Agitation, delirium, confusion, coma	Normal	HR ↑ BP ↑or labile Temperature ↑ RR ↑	Rarely oculogyric crisis	Increased	Bowel and bladder activity normal Dysphagia

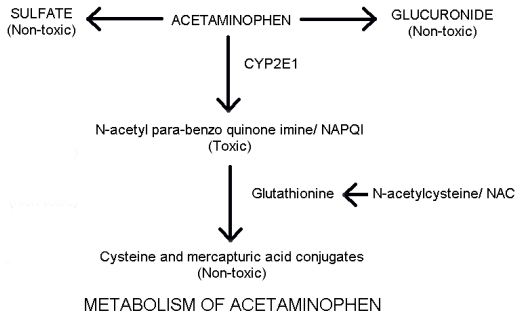
13.3. ACETAMINOPHEN

- Acetaminophen is also known as paracetamol or N-acetyl-p-aminophenol. Acetaminophen is the most widely available analgesic-antipyretic. Its over-the-counter availability has made it one of the most common poisonings.

PATHOPHYSIOLOGY:

- Less than 8% of paracetamol is metabolized into its toxic metabolite NAPQI by CYP2E1. NAPQI is detoxified by hepatic glutathione stores. With overdose hepatic glutathione gets depleted and NAPQI causes hepatic centrilobular necrosis.
- Induction of CYP2E1 by chronic alcoholism, isoniazid, rifampicin, phenytoin and barbiturates increases the risk of toxicity. Also patients with advanced age, malnutrition, liver disease prolonged fasting predispose to toxicity because of depletion of glutathione stores.
- Fatal dose: 10 gram (>150-250 mg/kg)

- Fatal period: 5-10 days



METABOLISM OF ACETAMINOPHEN

PRESENTATION:

Stage 1:
- It occurs on day 1.
- Anorexia, nausea, vomiting, diaphoresis, malaise occur.
- Subclinical rise in hepatic transaminases may be seen.

Stage 2:
- It occurs on day 2 and 3.
- Stage 1 symptoms abate and right hypochondriac pain and tenderness starts with or without hepatomegaly.
- Liver function tests are deranged.
- Nephrotoxicity may ensue.

Stage 3:
- It occurs on day 4 and 5.
- Stage 1 symptoms reappear.
- Hepatic failure, hypoglycemia, bleeding, encephalopathy, sepsis, renal failure and cardiomyopathy ensue.
- Lactic acidosis is seen and transaminases are increased in range of thousands.
- Liver biopsy shows centrilobular necrosis.
- Mortality is due to multi-organ failure.

Stage 4:
- It starts on day 5 and may persist for 3 weeks.
- Recovery or death occurs.

INVESTIGATIONS:
- Serum acetaminophen levels are done at four hours. Acetaminophen levels are then plotted on a nomogram (Rumack-Matthew nomogram) which helps in predicting risk of hepatotoxicity and indication of N-acetylcysteine.
- Liver function tests
- Urea, creatinine
- Lipase, amylase
- Arterial ammonia
- Blood group typing and cross-matching
- Ultrasound liver or kidneys

MANAGEMENT:
- GI decontamination preferably within four hours.
- Activated charcoal is given with four hours in a dose of 50-100 g OR 1 g/kg OR 10 times the weight of ingested poison as suspension in 4-8 oz of water.
- N-acetylcysteine:
    - Oral N-acetylcysteine:
        - It should be started within 8-10 hours and at maximum up to 24 hours.

        - Loading dose: 140 mg/kg diluted to about 5% with water, juice or soda STAT
        - Then 70 mg/kg every four hours for 17 total doses
    - Intravenous N-acetylcysteine:
        - It should be given if there is:
            - Altered mental status
            - GI bleeding/ obstruction
            - History of caustic ingestion
            - Potential fetal toxicity
            - Refractory vomiting
        - Loading dose: 150 mg/kg over one hour diluted in 200 ml dextrose 5% water
        - Then 50 mg/kg diluted in 500 ml dextrose 5% water over four hours
        - Then 100 mg/kg diluted in 1000 ml dextrose 5% water over 16 hours
- Other antidotes:
    - Methionine 2.5 g orally every 4 hourly for four doses
- Liver transplantation:
    - Indicated in case of acute liver failure, liver transplant is done.
    - Poor prognosis and need for transplantation is predicted by Modified King's College Criteria:
        - Arterial pH <7.3 or arterial lactate concentration >3.5 mmol/l after early resuscitation (4 h) or arterial lactate concentration >3.0 mmol/l after fluid resuscitation (12 h)
        - Presence of all of the following: INR >6.5, Creatinine >300 µmol/l and hepatic encephalopathy grade III or IV in a 24 hour period.

13.4. AMPHETAMINES

- Amphetamines produce CNS stimulation by increased sympathetic activity. These are widely used as illicit drugs/ recreational drugs.
- These include ephedrine, methamphetamine, methacathinone.

PRESENTATION:

- CNS effects: anxiety, tremulousness, agitation, seizures
- CVS effects: tachycardia, hypertension (may lead to intracranial hemorrhage, myocardial infarction or aortic dissection)
- Muscular effects: muscular hyperactivity, rhabdomyolysis
- Others: metabolic acidosis, dilated pupils, sweating

INVESTIGATIONS:

- Urine drug screen

MANAGEMENT:

- Stabilize patient. Maintain circulation, airway and breathing.
- Treat agitation: benzodiazepines, phenobarbital
- Treat hypertension: phentolamine, nitroprusside or labetalol
- Treat seizures: diazepam
- Treat arrhythmias: amiodarone or lidocaine

⇨ *Do not use a pure beta-blocker to treat hypertension in case of amphetamine poisoning – may lead to severe hypertensive crisis due to unopposed alpha-receptor action.*

13.5. BENZODIAZEPINES

- These drugs increase the effect of GABA at GABA-A receptor. These are used in cases of anxiety, insomnia, agitation, seizures, muscular spasms, pre-procedure sedation and drug withdrawal.
- These are safe for short-term use but long-term use may cause dependence.

PRESENTATION:

- Altered level of consciousness

- Usually normal vital signs
- Respiratory depression in very large doses

INVESTIGATIONS:
- Urea, creatinine, electrolytes
- Blood glucose
- Urine drug screen
- Investigations to rule out differential diagnosis e.g. hypoglycemia, meningoencephalitis

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Gastric lavage may not be needed.
- Treatment is supportive.
- FLUMAZENIL:
    - Indication: respiratory depression, prolonged sedation
    - Dose: 0.2 mg iv over 15 seconds and then repeat as 0.1 – 0.2 mg every minute till a total dose of 1 – 2 mg.
    - Avoid in case of epilepsy or concomitant TCA or epileptogenic drug ingestion.

13.6. BETA-BLOCKERS

- These include propranolol, atenolol, carvedilol, etc.
- They block beta receptors and have anti-adrenergic properties.

PRESENTATION:
- Hypotension, bradycardia
- Wide QRS
- Seizures
- Coma

INVESTIGATIONS:
- Clinical diagnosis

MANAGEMENT:
- Stop absorption: activated charcoal within one hour of ingestion
- Treat bradycardia and heart block: ATROPINE, ISOPROTERENOL, transcutaneous pacemaker.
- For persistent bradycardia: GLUCAGON 5 – 10 mg IV followed by 1 – 5 mg/ hour infusion.
- For severe cardiotoxicity: insulin glucose infusion

13.7. CALCIUM CHANNEL BLOCKERS

- Non-dihydropyridines: verapamil, diltiazem → decrease cardiac contractility and conduction
- Dihydropyridines: amlodipine, felodipine, nimodipine → cause vasodilation

PRESENTATION:
- Bradycardia, AV nodal block, hypotension, hyperglycemia

INVESTIGATIONS:
- Clinical diagnosis

MANAGEMENT:
- Stop absorption: activated charcoal within one hour of ingestion
- Treat bradycardia and heart block: ATROPINE, ISOPROTERENOL, transcutaneous pacemaker.
- Treat hypotension: calcium gluconate or chloride infusion
- For severe cardiotoxicity: insulin glucose infusion

- For refractory shock: methylene blue

13.8. CARBON MONOXIDE

- It binds to hemoglobin more avidly than oxygen and decreases oxygen binding capacity. It decreases deliver of oxygen to tissues.
- Toxicity usually occurs from improper heating system in cold seasons and automobile exhaust fires.

PRESENTATION:
- At low levels: headache, dizziness, abdominal pain, nausea
- At high levels: confusion, dyspnea, syncope, hypotension, coma, seizures

INVESTIGATIONS:
- Arterial or venous carboxyhemoglobin
- Arterial blood gases and saO2: may have false normal paO2 and saO2

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Hyperbaric oxygen i.e. 100% oxygen

13.9. COCAINE

- Cocaine inhibits reuptake of norepinephrine, serotonin, epinephrine and dopamine.

PRESENTATION:
- Sympathomimetic toxidrome
- Ischemic chest pain
- Hyperthermia
- Seizures
- Coma
- Cardiovascular collapse

INVESTIGATIONS:
- Urea, creatinine, electrolytes, CK, Troponin
- Urine and serum drug screen
- ECG
- Chest x-ray or CT chest: for suspected aortic dissection
- CT brain: for suspected intracranial hemorrhage

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Treatment is usually supportive.
- Iv fluids
- Treat hyperthermia: cooling, induce paralysis and ventilation
- Treat agitation: benzodiazepines, phenobarbital
- Treat hypertension: phentolamine, nitroprusside or labetalol
- Treat seizures: diazepam
- Treat arrhythmias: amiodarone or lidocaine

⇨ *Do not use a pure beta-blocker to treat hypertension in case of cocaine poisoning - may lead to severe hypertensive crisis due to unopposed alpha-receptor action.*

13.10. CORROSIVES

Corrosives or caustics include:

- Acids:
  - Hydrochloric acid – usually used as a descaling agent
  - Sulfuric acid – usually used in car batteries
  - Nitric acid – usually used as metal cleaner
  - Hydrogen fluoride – usually used for rust removal
- Alkalis:
  - Sodium hydroxide – used as liquid lye
  - Hypochlorite – used as bleach

MECHANISM OF ACTION:

These are usually ingested for suicidal purposes and sometimes accidentally. Inhalation of volatile acids may cause irritation, laryngeal edema or ARDS.

- Acids cause coagulative necrosis of local tissues. These lead to edema, erythema, mucosal sloughing and ulceration of skin and mucosa. Later on stricture may form.
- Alkalis cause liquefactive necrosis of tissues. Carcinomas can occur after a long time.

PRESENTATION:

- Pain in throat and heartburn
- Hematemesis
- Dysphagia, dyspnea

MANAGEMENT:

- Stabilize patient. Maintain circulation, airway and breathing.

In case of ingestion:

- Dilute the ingested amount:
  - Give a glass of water to drink.
  - Do not give an alkali or neutralizing agent. It will neutralize acid but cause intense generation of heat which worsens damage.
- Nasogastric intubation is contraindicated.
- Assess extent of injury:
  - Perform upper GI endoscopy on day or 2.
  - Patients with mild lesions can be discharged.
  - Patients with severe lesions should undergo surgical gastrostomy.
- Patients who present after 72 hours:
  - Gastrostomy if severe dysphagia.
  - Endoscopy and dilatation of stricture after 3 weeks.

In case of skin or eye contact:

- Wash area or eye with water for 15 minutes.
- Give topical anesthetics for eye.
- Take plastic surgery or ophthalmologist opinion if needed.

13.11. CYANIDE

- It is one of the most rapid and lethal poisons.
- Its poisoning occurs mainly via inhalation of smoke during fires or suicidal or homicidal ingestion. It can also accumulate in body from metabolism of sodium nitroprusside during prolonged iv infusion.
- It disrupts the electron transport chain and prevents formation of ATP. The cellular hypoxia leads to lactic acidosis.

PRESENTATION:

- Tachycardia, tachypnea, hypertension

- Headache, dizziness, anxiety, lethargy, zeizures, coma

INVESTIGATIONS:
- Blood levels
- Lactate levels
- Elevated paO2 and saO2 in venous blood

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Give iv fluids.
- Give vasopressor or inotropic support.
- Specific treatment:
    - Amyl nitrite pearls in nose
    - Iv sodium nitrite: it induces formation of methemoglobin which binds to CO
    - Sodium thiosulfate: induces formation of methemoglobin
    - Hydroxycobalamin: binds to cyanide to form harmless cyanocobalamin (vitamin B12)

13.12. DICHLORODIPHENYLTRICHLOROETHANE (DDT)

- It is classified as organochlorine compounds.
- It is used as an insecticide or pesticide.

PRESENTATION:
- Local features: irritation of eyes, skin or nose
- Nervous system features: restlessness, spasms, seizures, paralysis, respiratory failure
- Cardiac dysrhythmias
- Pulmonary features: cough, dyspnea

INVESTIGATIONS:
- Urea, creatinine, electrolytes, CBC
- ABGs/ VBGs
- ECG
- Urine D/R
- Urine and serum toxicology screen

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing. Mechanical ventilation if needed.
- Gastric lavage
- Consider multiple-dose activated charcoal. May also use cholestyramine.
- Iv hydration
- N-acetylcysteine in case of liver injury
- Avoid giving adrenaline or other sympathomimetics
- Atropine and oximes are of no benefit
- Antiepileptics

13.13. DIGITALIS

- It is a cardiac glycoside used for refractory heart failure to relieve symptoms and decrease hospitalizations.
- It has a very narrow therapeutic index and exhibits significant drug interactions.

PRESENTATION:
- Extracardiac: Nausea, vomiting, drowsiness, yellow vision (xanthopsia)
- Cardiac: palpitations, shortness of breath, syncope, syncpe, bradycardia

INVESTIGATIONS:
- Electrolytes: hypokalemia predisposes to digitalis toxicity, hyperkalemia indicates digitalis toxicity

- Renal function tests
- Serum digoxin levels
- ECG: scooped ST depressions (Dali's sign), sinus bradycardia, AV blocks, bidirectional ventricular tachycardia

MANAGEMENT:
- Iv fluids
- Activated charcoal or cholestyramine for acute ingestion
- For hyperkalemia: avoid iv calcium, give insulin + glucose and sodium bicarbonate
- Digoxin Fab fragments if potassium >5.0 meq/L
- Hemodialysis
- Correct hypomagnesemia
- For ventricular arrhythmias: phenytoin, lidocaine, avoid cardioversion

13.14. ETHYLENE GLYCOL

- It is used in anti-freeze liquids of car radiator.
- It is usually ingested for suicidal purposes or as a cheaper alternative to alcohol.
- It is metabolized to glycolic acid and oxalic acid. Glycolic acid causes metabolic acidosis while oxalic acid binds to calcium and precipitates in kidney causing renal failure.

PRESENTATION:
- Within 30 minutes to 12 hours: CNS depression
- Within 12 hours to 24 hours: cardiovascular effects like tachycardia, heart failure, pulmonary edema
- Within 24 hours to 72 hours: renal failure (ATN)

INVESTIGATIONS:
- ABGs/ VBGs
- Urea, creatinine, electrolytes, serum osmolarity, osmolar gap, ketones
- Lactate: may be falsely high due to glycolic acid
- Urine D/R: shows envelope-shaped crystals of calcium oxalate
- Ethanol and ethylene glycol levels

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Decontamination: nasogastric lavage within one hour of ingestion, no use of activated charcoal
- For acidosis: sodium bicarbonate
- Antidotes:
    - Ethanol
    - Fomepizole
- Thiamine and pyridoxine increase breakdown of toxic metabolites
- Hemodialysis

13.15. HYPOGLYCEMIC DRUGS

- Insulin and secretagogues (e.g. sulfonylureas) are the most common anti-diabetic medications that result in hypoglycemia.

SYMPTOMS AND SIGNS:
- Are those of hypoglycemia.

TREATMENT:
- Give high sugar and carbohydrate containing foods and drinks.

- For severe hypoglycemia, or if the patient is unable to take orally → D50W 50 ml intravenously and repeat if needed. Give D5W or D10W solutions intravenously to keep blood sugar > 70 – 80 mg/dl.
- For sulfonylureas and related drugs use OCTREOTIDE 50 – 100 µg subcutaneously every 6 – 12 hours.
- Observe asymptomatic patients for at least 12 hours.
- Other alternatives could be steroids

13.16. METHANOL

- It is also known as wood alcohol.
- It is used in solvents, photocopy fluids, record cleaning solutions and paint removers.
- It is also a contaminant of boot leg whiskey (moon-shine whiskey).
- It is usually ingested for suicidal purposes or as a cheaper alternative to alcohol.
- It is metabolized to formaldehyde by alcohol dehydrogenase which is then changed to formic acid by aldehyde dehydrogenase. Formic acid causes metabolic acidosis and damages retina and basal ganglia particularly putamen.

PRESENTATION:
- Initially: confusion, drowsiness, headache
- Within 12 hours: increased osmolality
- After 12 – 24 hours: high anion gap metabolic acidosis, tachypnea, confusion, convulsions, dyskinesias, coma, visual disturbances (blurring, field defects, snow-storm or snow-field vision, blindness)

INVESTIGATIONS:
- ABGs/ VBGs
- Urea, creatinine, electrolytes, serum osmolarity, osmolar gap, ketones, lactate
- Urine D/R: shows envelope-shaped crystals of calcium oxalate
- Ethanol and methanol levels

MANAGEMENT:
- Stabilize patient. Maintain circulation, airway and breathing.
- Decontamination: nasogastric lavage within one hour of ingestion, no use of activated charcoal
- For acidosis: sodium bicarbonate
- Antidotes:
    - Ethanol
    - Fomepizole
- Folic acid: increases breakdown of toxic metabolites
- For severe toxicity: hemodialysis

13.17. OPIATES/ OPIOIDS

PATHOPHYSIOLOGY:

- Opioid over-dose → CNS respiratory depression

PRESENTATION:

- Altered level of consciousness
- Respiratory depression
- Miosis

INVESTIGATIONS:

- Diagnosis is usually clinical
- Monitor respiratory status with pulse oximetry and arterial blood gases

TREATMENT:

- Maintain airway and give ventilator support.
- Avoid gastric lavage.
- NALOXONE 0.04 – 2 mg iv with doses repeated as needed.
- Patient can be disposed off if he or she is alert for 4 – 6 hours after last naloxone dose.

13.18. ORGANOPHOSPHATE COMPOUNDS

PATHOPHYSIOLOGY:

- Organosphosphates act as anti-cholinesterases compounds → bind to acetylcholinesterase and stop degradation of acetylcholine → increase acetylcholine → symptoms of acetylcholine excess

MODE OF ACQUISITION:

- Inhalation
- Skin contact
- Ingestion (usually suicidal)

PRESENTATION:

- Muscarininc symptoms: remembered by mnemonics
  - ***SLUDGE***: Salivation, lacrimation, urination, diarrhea, GI upset, emesis
  - ***DUMBELLS***: diaphoresis and diarrhea, urination, miosis, bradycardia, bronchospasm and bronchorrhea, emesis, excess lacrimation, salivation
- Nicotinic symptoms:
  - Tachycardia, mydriasis, hypertension, sweating
  - Muscle weakness, paralysis, fasciculations
- CNS effects:
  - Confusion, agitation, coma, respiratory failure

INVESTIGATIONS:

- CBC
- Plasma butyrylcholinesterase assay
- RBC acetylcholinesterase assay
- ECG
- Chest x-ray
- Arterial blood gases

TREATMENT:

- Stabilize circulation, airway and breathing
- Decontamination:
  - Inhalation or skin exposure:

        - Wear gloves
        - Remove person from area of contamination
        - Remove soiled clothes
        - Wash patient with soap and water
    - Ingestion:
        - Gastric lavage
        - Administer activated charcoal if presents within one hour
- Take CBC and serum cholinesterase
- Antidotes:
    - Atropine 1 – 2 mg iv every 5 – 15 minutes till signs of atropinization. Once atropinized and stable, give 10 – 20% of the maximum dose given as an infusion per hour.
        - Signs of atropinization: dry skin, pulse >70/min, dilated pupils
        - Signs of atropine toxicity:
            - Warm dry skin, dilated pupils, psychosis, flushing
            - Mnemonic: ***As dry as a bone, as hot as a hare, as blind as a bat, as mad as a hatter, as red as a beet***.
        - Treatment may be continued for 3 days
    - Glycopyrrolate:
        - Mainly decreases secretions.
        - Used as an adjunct to atropine.
    - Pralidoxime:
        - Loading dose 30 mg/ kg (roughly 2 g) iv over 30 minutes
        - Infusion 8 – 10 mg/ kg/ hour (roughly 0.5 – 1 g/ hour) till recovery or seven days
- Monitor and record pulse rate, bood pressure, pupil size, presence of sweat and breath sounds.
- Assess flexor neck strength continuously (loss of neck strength is an early feature of intermediate syndrome).
- Diazepam 5 – 10 mg iv as needed for sedation.

13.19. PARAPHENYLENE DIAMINE (PPD)

- It is commonly known as kala pathaar. It is a component of hair dye.

PRESENTATION:

- Angioneurotic edema especially laryngeal and facial edema: pain in throat, dysphagia, dyspnea, stridor
- Rhabdomyolysis: muscle aches, dark urine,
- Severe metabolic acidosis
- Electrolyte disturbances: hyperkalemia, hyperphosphatemia, hypophosphatemia
- Acute renal failure

INVESTIGATIONS:

- CBC, urea, creatinine, electrolytes

MANAGEMENT:

- Treatment is supportive
- Intubation and ventilation for laryngeal edema
- Manage electrolyte disturbances

13.20. SALICYLATE OVERDOSE

- It results from acute or chronic over-dosage of acetylsalicylic acid (aspirin).
- Toxicity occurs on taking >100 mg/ kg of aspirin.

PRESENTATION:

- Nausea, vomiting, tinnitus, tachypnea, hyperpnea, malaise
- Severe: lethargy, convulsions, coma, non-cardiogenic pulmonary edema

INVESTIGATIONS:

- Urea, creatinine
- Electrolytes
- Blood glucose
- Arterial blood gases: may show early respiratory alkalosis followed by metabolic acidosis
- Salicylate concentrations

MANAGEMENT:

- Activated charcoal 50 – 100 g if presents within one hour.
- Alkaline diuresis for symptomatic individuals with salicylate concentrations >40 mg/ dL.
    - Use 150 mEq of sodium bicarbonate diluted in 850 mL 5% dextrose water and give at 10 – 15 ml/ kg/ hour till diuresis. Then continue at 2 – 3 ml/ kg/ hour.
    - Alkalinization increases aspirin excretion in urine.
- Maintain serum potassium above 4 mEq/ L.
- Mechanical ventilation if in respiratory failure. Hyperventilate to compensate for metabolic acidosis.
- Monitor for cerebral edema and seizures.
- Hemodialysis if concentration >100 mg/ dL in acute poisoning.

13.21. TRICYCLIC ANTI-DEPRESSANTS (TCA)

- These drugs inhibit reuptake of serotonin and norepinephrine. They also have antimuscarinic activity.
- They include amitriptyline, clomipramine, doxepin, imipramine, desipramine and nortriptyline.
- These are commonly used as anti-depressants.

PRESENTATION:

- CNS depression, tachycardia, hypotension, dilated pupils, dry mucous membranes, urinary retention, seizures

INVESTIGATIONS:

- VBGs for bicarbonate
- Potassium
- ECG: wide QRS, dysrhythmias

MANAGEMENT:

- Stabilize patient. Maintain circulation, airway and breathing.
- Intubate patients with altered level of consciousness.
- Decontamination: nasogastric lavage, activated charcoal
- Alkalinization therapy: hyperventilation, iv sodium bicarbonate for 12 – 24 hours
- For hypotension: use norepinephrine
- For ventricular arrhythmias: use lidocaine
- For seizures: use benzodiazepines

13.22. VALPROIC ACID

- It is used as an anti-epileptic agent.
- It inhibits sodium and calcium channels and also increases action of GABA.
- It causes fatty infiltration of liver and hyperammonemia.

PRESENTATION:

- Tremors, ataxia, sedation, abdominal pain, altered level of consciousness, coma,
- May develop pancytopenia

INVESTIGATIONS:

- CBC, LFTs, ammonia levels, lipase
- Valproate levels

MANAGEMENT:

- Supportive care
- Decontamination: nasogastric lavage, activated charcoal
- L-carnitine in case of hyperammonemia

13.23. ENVENOMATIONS

13.23.1. SNAKE-BITES

- Snake bite is a very important medical emergency in Asia. It can result in death as well as disability in young adults.
- Most of the bites take place while doing activities in fields e.g. grass-cutting, farming, plantation, fishing, etc.

COMMON SNAKES IN PAKISTAN:

- Russel's viper
  - Usually injects 60 mg of venom in each bite.
  - Usually cause consumption coagulopathy.
- Cobra
  - Up to 50% of bites are dry bites (no venom injected).
  - Usually injects 60 mg of venom in each bite.
  - Usually cause neurotoxicity.
- Krait
  - Injects less toxin but the bite is difficult to differentiate from that of cobra.
  - Usually cause neurotoxicity.
- Saw-scaled viper
  - Amount of venom injected with each bite is uncertain.
  - Usually cause consumption coagulopathy.

PATHOPHYSIOLOGY:

- Cobra venom inhibits binding of acetylcholine to post-synaptic nicotinic receptor.
- Krait venom inhibits release of acetylcholine from pre-synaptic nerve.

CHARACTERISTIC FEATURES OF SNAKE BITE ENVENOMING:

- Coagulopathy:
  - Indicated by a 20 minute whole blood clotting time.
  - May be overt with bleeding from different sites e.g. gum bleeding, hemoptysis, hematemesis
- Neurotoxicity:
  - Ptosis, loss of neck lift, flaccid paralysis (usually descending), respiratory failure
- Local features:
  - Infection, cellulitis, compartment syndrome

MANAGEMENT:

- Estimate following:
  - Time of bite:
  - Activity at the time of bite:
  - First aid activities taken:
- Indications for administering anti-snake venom (ASV):
  - Incoagulable blood determined by 20 minute whole blood clotting tests
  - Visible neurological signs such as ptosis, ophthalmoplegia or other evidence of descending paralysis
  - Evidence of current systemic bleeding

- Administration of ASV:
  - Test dose should not be given as it wastes time and does not predict reactions.
  - Prophylactic pre-medications to prevent reactions may be used: hydrocortisone, anti-histamine, subcutaneous adrenaline.
  - There are two types of ASV:
    - Lyophilized ASV:
      - It is imported from India.
      - It does not refrigeration for storage.
    - Liquid ASV:
      - It is synthesized at NIH Islamabad.
      - It has more adequate coverage of local snakes.
      - It needs refrigeration for storage.
  - Each ASV vial neutralizes 6 mg of snake venom.
- Dose of ASV:
  - Initial dose:
    - 8 – 10 vials for Russel viper and cobra bites. Administer over one hour or as a continuous infusion.
    - 4 vials for saw-scaled vipers.
  - Dose is same in children as the amount of venom injected is the same.
  - ASV is not contraindicated in pregnancy.
- Coagulopathy envenomation:
  - Monitor 20WBCT 6 hourly and administer ASV every 6 hours.
- Neurotoxic envenomation:
  - ASV:
    - Give ASV. Review after one hour.
    - If symptoms worsen then give a second dose over one hour. If not worsened then a second review after 2 hours and give dose if symptoms worsened.
  - Anticholinergics:
    - Check single breath count or length of time an upward gaze can be maintained.
    - If weakness at presentation then give 1.5 mg NEOSTIGMINE IM with 0.6 mg of ATROPINE iv.
    - Assess every 10 minutes.
    - If improvement occurs then give 0.5 mg NEOSTIGMINE and ATROPINE every 30 minutes.
- Adverse reactions to ASV:
  - Itching, urticaria, anaphylactoid reactions.
  - Suspend ASV temporarily at the first indication of reaction.
  - Drug of choice ADRENLINE 0.5 mg 1:1000 IM. If not improving a second dose may be given after 30 minutes.
  - Also give 100 mg HYDROCORTISONE iv + Antihistamine e.g. PHENIRAMINE maleate 22.5 mg iv or PROMETHAZINE 25 mg IM or CHLORPHENIRAMINE maleate 10 mg iv.
  - ASV can be resumed if reaction improved.
- General management:
  - Allay anxiety and fear.
  - Do not apply tourniquet.
  - Do not cut the wound area.
  - Ask patient to move as little as possible and lay straight.
  - Whole blood should not be used as treatment unless severe bleeding.
  - Use paracetamol for pain and not aspirin.
  - Tetanus vaccination.
  - Antibiotics if local necrosis or any first aid measures used.
  - Ventilator support if needed.
  - Surgery – debridement of necrotic tissue or fasciotomy in case of compartment syndrome.

15. ENVIRONMENTAL MEDICINE

15.1. COLD RELATED ILLNESSES

15.1.1. FROST-BITE

"It is the freezing of fluids in the interstitial spaces due to prolonged exposure to freezing temperatures."

PATHOPHYSIOLOGY:

- Cold exposure of skin → cold induced vasoconstriction → insufficient heat to prevent cold induced crystallization of tissues → crystallization damages cells and causes thromboemboli in microcirculation → nerosis and gangrene.
- Asides from above, there is also cold induced damage to cells and reperfusion injury on rewarming. It mostly involves hands, feet, ears and nose.

SYMPTOMS:

- Cold feeling in exposed tissue; paresthesias; numbness (indicates establishing frost-bite); loss of dexterity of limb; joint pain.

SIGNS:

- Soft palpable skin; hard skin (late); pallor or cyanosis; hyperemia; necrosis; gangrene.

COMPLICATIONS:

- Permanent loss of sensation; local infection; necrosis; compartment syndrome; amputation.

MANAGEMENT:

- Maintain airway, breathing and circulation.
- Rewarm the area using circulating warm water (40 – 42 degrees centigrade).
- Give pain relief.
- Avoid early amputation until tissues have well-demarcated.
- Elevate the area with splinting.
- Change dressings 2 – 4 times a day.
- Aspirate clear blisters.
- Apply topical aloe vera cream.
- Give tetanus prophylaxis.
- Antibiotics should only be used if infection occurs.
- Thrombolysis with tPA within 24 hours of thawing improves outcomes in suitable patients.
- Administraton of vasodilators like iloprost, buflomedil, pentoxifylline, etc.
- Debridement of tissues. Skin grafting if needed. Physical rehabilitation.

15.1.2. TRENCH FOOT

aka Immersion foot

"It is a condition caused by prolonged exposure of feet to damp cold environment. "

SYMPTOMS AND SIGNS:

- Tingling/ itching/ pain/ heaviness in feet, swelling; cold blotchy skin; red or cyanosed, dry tender feet (escpecially after rewarming); blisters; peeling of skin; ulcers or open sores.

PREVENTION:

- Keep feet clean and dry; wear dry socks and shoes.

TREATMENT:

- Apply warm packs or soak feet in warm water for 5 minutes. If untreated it can lead to amputation.

15.1.3. SNOW BLINDNESS

aka photokeratitis/ ultraviolet keratitis

"It is a sun burn of eyes caused by reflection of sunlight off snow or water."

- Similar condition may also develop after watching solar eclipse without protective goggles or by watching welding arcs.

SYMPTOMS AND SIGNS:

- Pain and redness of eyes, blurring of vision, gritty sensations, swelling in eyes, headache, temporary loss of vision.

TREATMENT:

- Treatment is supportive, artificial tears, analgesics, topical antibiotics if secondarily infected, cold eye-patches. Do not rub eyes.

PEVENTION:

- Wearing sun-glasses or goggles.

15.2. HEAT STRESS/ HEAT RELATED ILLNESSES

The spectrum of heat-related illness comprises the following:

1. Heat rash
2. Heat edema
3. Heat cramps
4. Heat tetany
5. Heat syncope
6. Heat exhaustion
7. Heat stroke

- Heat-related illness can be prevented by simple measures:
- Remaining in cool shaded places during hot weather
- Avoidance of exercise or physical work in hot weather.
- Avoidance of exposure to sun.
- Drinking plenty of fluids/ electrolyte solutions
- Avoid wearing excess clothes. Wear light-colored loose clothings.
- Cover head when out in the sun. Use small towels/ wide-brimmed hats/ umbrella.
- Wear sun-glasses.
- Wear protective heavy sun-screen.
- Do not remain or leave anyone inside a closed car parked in hot weather.
- Avoid medicines which decrease sweating, impair heat-loss or increase dehydration (anti-histamines, decongestants, amphetamines, anticholinergics, antipsychotics, anti-epileptics, beta-blockers and diuretics.
- Avoid caffeine and alcohol.
- Infants, young children, elderly, febrile patients, bed-bound patients and patients unable to take by mouth should take special precautions.
- Use of a heat index chart.

15.2.1 HEAT RASH

Aka miliaria OR sweat rash OR prickly heat

"Miliaria is an obstruction of sweat glands occurring on heat exposure."

AT RISK:

- Hot humid weather; conditions with profuse sweating; wearing excessive clothes; bed-bound patients (on backs)

RASH:

- Rash appears in skin folds and on the body as itchy small blisters or tiny red papules. Sometimes pustules may form.

PATHOPHYSIOLOGY:

- Overgrowth of staphylococcus epidermidis → secretions that block sweat gland ducts → accumulation of sweat behind the block

TREATMENT:

- Avoidance of sweating; avoidance of itching/ irritating skin; remaining in cool less humid places; avoidance of excess clothes or friction from clothes; cold water compresses; proper ventilation; calamine lotion; emollients; mild topical steroids (for severe cases); anti-staphylococcal antibiotics (if secondarily infected).

15.2.2. HEAT EDEMA

"It is appearance of edema on dependent parts of the body due to heat-related vasodilation and inadequate salt excretion."

15.2.3. HEAT CRAMPS

"Heat cramps are painful involuntary spasms of large muscles occurring from salt water losses in hot weather or on strenuous exercises."

AT RISK:

- Those who work or exercise in hot weather.

AREAS INVOLVED:

- They typically occur in arms, legs, back and abdomen.

TREATMENT:

- Drinking juices or electrolyte containing drinks; intravenous hydration with electrolytes; gentle massage and stretching of affected muscles; rest and don't resume activity for several hours after cramps subside.

15.2.4. HEAT TETANY

"It is appearance of hyperventilation, numbness/tingling, respiratory problems or muscle spasms when exposed to short periods of stress in intense hot weather."

15.2.5. HEAT SYNCOPE

"Heat syncope is a fainting (syncope) or dizziness episode that occurs on prolonged standing or on rising in hot weather."

SYMPTOMS:

- Light-headedness, dizziness, fainting

TREATMENT:

- Sitting or lying for some time; oral or intravenous hydration.

15.2.6. HEAT EXHAUSTION

"It is a lethargic state which occurs on excessive sweating in hot weather leading to fluid and electrolyte losses"

SYMPTOMS/ SIGNS:

- Heavy sweating; fatigue; generalized weakness; dizziness; confusion; nausea and vomiting; clammy moist skin; pale complexion; muscle cramps; fever; fast and shallow breathing; headache; dilated pupils.

TREATMENT:

- Sitting or lying for some time in cool shaded area; drinking fluids, juices and electrolyte solutions; iv hydration; taking a cool shower/bath.

15.2.7. HEAT STROKE

"It is a body temperature >106^{o}F (41.1^{o}C) which results in neurological dysfunction."

- **Exertional heat stroke:** seen usually in young people who are physically active in hot weather.
- **Non-exertional heat stroke:** affects people who are bed-bound i.e. very young, elderly, denilitated.

PATHOPHYSIOLOGY:

- Excessive heat gain overwhelms body's thermostatic mechanisms → denaturation of body proteins and liquefaction of lipids → cardiovascular instability → multi-organ failure.

SYMPTOMS/ SIGNS:

- Throbbing headache; dry, hot and red skin (sweating stops); dizziness; nausea; lethargy; drowsiness or unconsciousness; dyspnea; weakness; seizures; hyperthermia (up to 106^{o}F); constricted pupils; tachycardia; tachypnea; signs of stroke.

TREATMENT:

- Aim of treatment is rapid cooling of core body temperature (duration of hyperthermia determines outcome).
- Cooling is best initiated at the site of heat stroke before transportation.
- Rectal temperature is the most accurate method of measuring core body temperature.
- As first aid remove the person from the hot environment and place in a cool shaded area. Remove restrictive clothing and elevate feet. Spray water on the body and wet clothes with cool water. Place ice-packs in the axilla and groin. Transport immediately to nearest hospital.
- Give supplemental oxygen.
- Lower the temperature to about 39^{o}C to avoid rebound hyperthermia.
- Start on dextrose solution and watch for hypoglycemia.
- Reduce temperature by 0.2^{o}C / min to about 39^{o}C.
- Antipyretics have no role in treatment.
- Methods for rapid cooling:
    - **Ice-water immersion:** Immerse patient in ice-water.
    - **Evaporation:** Remove patient's clothes, spray the body with water and place in front of a fan.
    - **Gastric lavage with ice water**
    - **Cold intravenous fluids**
    - **Cooling blankets**

- Give intravenous fluids.
- Watch for rhabdomyolysis, electrolyte disturbances, hepatic injury, pulmonary edema and acute renal injury.

15.3. ELECTRIC INJURY

"An electrical injury is damage to skin or internal organs after exposure to an electrical current."

- High-voltage injury (>1000 volts)
- Low-voltage injury (<1000 volts)

- **True electrical injuries:** electricity runs through the body via an entry and exit wound. These can include burns or deeper tissue injuries in the form of edema and compartment syndrome.
- **Flash injuries:** electrical arcs directly cause burns on the skin.
- **Flame injuries:** electrical arcs may ignite flames in clothes and nearby objects which lead to burns.
- **Lightning injuries:** very high voltage current such as that from lightning strikes the body.
- **Mechanical injuries:** electrical current may lead to falls or violent muscle contractions.

PRESENTATION:
- Simple tingling sensations; electrical burns; compartment syndrome; cardiac dysrhythmias; rhabdomyolysis; acute renal failure; fall and mechanical injuries like fractures.

INVESTIGATIONS:
- CBC, UCE, LFT's, urine D/R, urine for myoglobin
- ECG should be done in all patients.
- Imaging studies if there is fall/ tetany/ injuries.

MANAGEMENT:
- Manage as trauma patients. Stabilize airway, breathing and circulation. Do trauma survey.
- Treat burns.
- Hydrate aggressively (normal saline or ringer's lactate) and maintain urine output >0.5 ml/kg/hour (>1 ml/kg/hour in case of myoglobinuria). Add diuretics if needed.
- Use Parkland formula for fluid replacement if there are superficial burns.
- If myoglobinuria is suspected, give bicarbonate 1 – 2 meq/ kg.

⇨ ***Superficial appearance of an electrical burn does not indicate the extent of tissue damage***.

15.4. CAISSON'S DISEASE

Aka the bends, decompression sickness

"It is a condition in which dissolved nitrogen in blood and tissues under high pressure forms bubbles upon sudden decompression."

PATHOGENESIS:

- As person descends underwater pressure of breathing air increases → increased dissolution of nitrogen in blood → if diver ascends too rapidly → nitrogen decompresses and forms bubbles in tissues and blood

PRESENTATION:

- Fatigue, pain in muscles and joints, chest pain, dyspnea.
- Type I: affects skin, joints and muscles.
- Type II: affects brain, spinal cord and lungs.

TREATMENT:

- Administer 100% oxygen.
- Maintain circulation, airway and breathing.
- Treat symptoms.
- Recompression therapy.
- Prevention: limit depth and duration of dives; avoid rapid ascents.

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8. SPECIAL BONUS TOPICS

Note: The following topics have been added on popular demand and will be properly incorporated in the second edition of the book.

8.1. VITAMIN D DOSING

- 25(OH) D is the best test to assess vitamin D stores.
- D2 = ergocalciferol, D3 = cholecalciferol. Both are inactive forms.
- Current dietary recommendations: 1500 – 2000 IU daily (highest level 4000 IU/ day)
- One International unit (IU) of vitamin D is equal to 0.025 microgram of D2 or D3.
- Treatment dose in case of severe deficiency (<10 ng/ mL):
    - Give 50,000 IU orally once weekly for 2 – 3 months (this is equivalent to 1/4th of the commercially available vitamin injection)
- Treatment dose in case of milder deficiency (11 – 2 ng/ mL):
    - Lower doses for shorter durations

8.2. MDR TUBERCULOSIS TREATMENT REGIME

Table 3.17. FIVE CLASSES OF ANTI-TUBERCULOUS DRUGS

GROUP 1 FIRST-LINE ORAL	GROUP 2 SECOND-LINE INJECTABLE	GROUP 3 FLUORO-QUINOLONES	GROUP 4 ORAL BACTERIO-STATIC	GROUP 5 UNCLEAR DRUGS
Isoniazid Rifampicin Ethambutol Pyrazinamide Rifabutin	Kanamycin Amikacin Capreomycin Streptomycin	Levofloxacin Moxifloxacin Ofloxacin Gatifloxacin	Para-aminosalicylic acid Cycloserine Terizidone Ethionamide Prothionamide	Clofazimine Linezolid Amoxicillin-clavulanate Thiacetazone Clarithromycin Imipenem-cilastatin High dose isoniazid

Choosing an MDR treatment regime:

1. Choose one injectable drug from group 2: kanamycin or amikacin based on drug-susceptibility testing (DST).
2. Choose a fluoroquinolone: levofloxacin or moxifloxacin based on DST.
3. Choose two drugs from group 4: ethionamide, cycloserine, or PAS. DST not reliable.
4. Choose group 1 drugs: pyrazinamide (add routinely if not intolerant or resistant) or ethambutol (if likely effective).
5. Choose two drugs from group 5 if the number of total effective drugs from group 2 – 4 is not four.

Continue injectables for at least 8 months or at least 4 months after becoming culture-negative, whichever is longer. Treatment should continue for a minimum of 20 months or at least 18 months after becoming culture-negative whichever is longer.