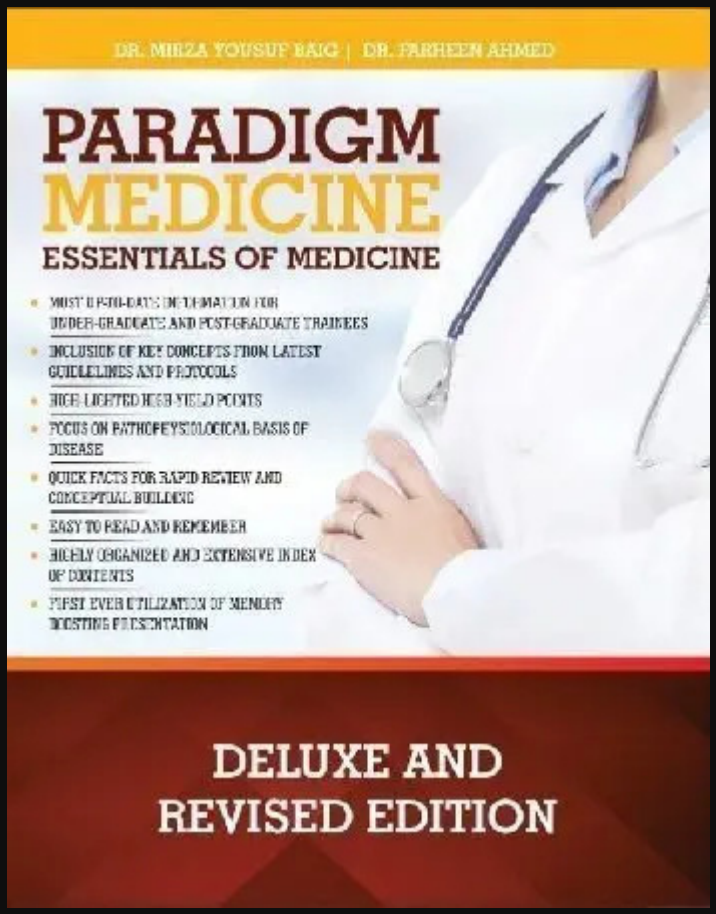
DR. MIRZA YOUSUF BAIG | DR. FARHEEN AHMED
PARADIGM
MEDICINE
ESSENTIALS OF MEDICINE
DELUXE AND
REVISED EDITION

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4. CARDIOLOGY

4.1. ELECTROCARDIOGRPAHY

"Electrocardiography is recording of electrical activity of heart from the heart surface."

- P = atrial depolarization
- PR interval = Time taken for impulse to reach AV node from SA node
- QRS wave = Ventricular depolarization
- T = Ventricular repolarization
- U = Delayed repolarization of Purkinje fibres

4.1.1. IDENTIFICATION OF PATIENT

- Check and identify whether the ECG belongs to the same patient.
- Always compare with old ECG if available.

4.1.2. CALIBRATION

- The ECG paper consists of 1 mm × 1 mm small boxes.
- The horizontal axis represents the time in milliseconds and the vertical axis represents the voltage in millivolts.
- Usual calibration is speed of 25 mm/sec (1 small box = 0.04 seconds OR 40 milliseconds) and voltage is 10 mm/ mV (1 small box = 0.1 millivolts).
- Calibration can be changed depending on requirements.

4.1.3. REGULARITY

- Check R-R interval by marking a piece of paper and sliding the paper to see if subsequent R waves coincide with same marks.

4.1.4. RATE

- For a regular rhythm, rate can be calculated by

$$\textbf{Rate in beats per minute} = \frac{\textbf{1500}}{\textbf{Number of small boxes in between two consecutive R waves}}$$

OR

$$\textbf{Rate in eats per minute} = \frac{\textbf{300}}{\textbf{Number of large boxes in between two consecutive R waves}}$$

- For an irregular rhythm, take a six-second strip (=30 large boxes) or long lead/10-second strip (=50 large boxes). Count the number of R waves in the strip and multiply by 10 (in case of 6-s strip) or 6 (in case of 10-second strip) to obtain the number of R waves per 60-second strip (i.e. rate).
- If atrial rate is to be calculated then use P waves instead of R waves.

4.1.5. RHYTHM

Rhythm can be assessed by looking at:

- P wave morphology
- Heart rate
- QRS width
- P-QRS correlation

Sinus:

- Sinus rhythm can be judged by an upright smooth P wave of good height and width (at least 2 x 2 mm) in lead II.
- A QRS follows each P wave (except in AV blocks). QRS is narrow (except in case of aberrancy or accessory pathway). Rate is usually in between 60 – 100 beats/min.

Atrial:

- An abnormally shaped P (labeled P') is present which does not satisfy the criteria for sinus rhythm. P' wave is upright in case of high atrial rhythm and inverted in case of low atrial rhythm. QRS is narrow (except in case of aberrancy or accessory pathway). Rate is usually in between 60 – 100 beats/min.

Nodal/ Junctional:

- A nodal rhythm can present as:
- Absent P wave with narrow QRS.
- Narrow QRS with retrograde P waves. The retrograde P waves may present just at the beginning of QRS, in between QRS or in between QRS and T waves.
- QRS is narrow (except in case of aberrancy or accessory pathway). Rate is usually in between 40 - 60 beats/min.

Ventricular:

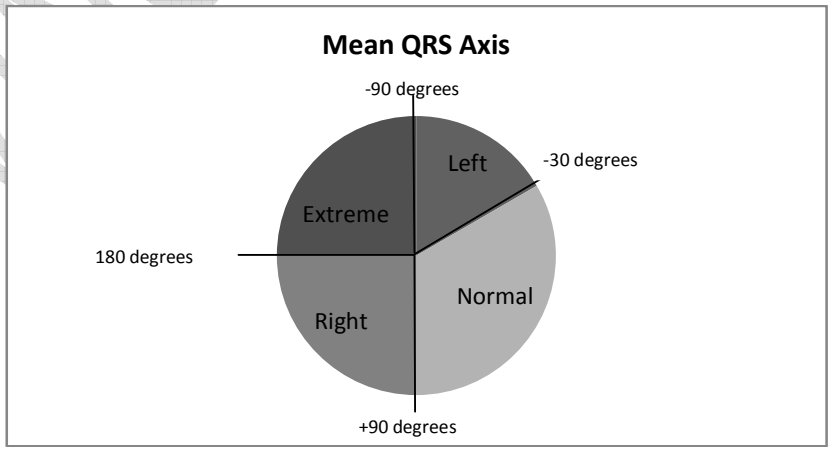
- There is no P – QRS correlation.
- QRS is usually wide.
- Rate is usually <40 beats/ min.

4.1.6. AXIS

- Mean QRS vector is -30 to +90 degrees.
- **Using leads I, II and III:**
- + means R wave amplitude is more than S wave amplitude.
- - means R wave amplitude is less than S wave amplitude.

Table 4.1. DETERMINING AXIS USING QRS IN BIPOLAR LEADS

	I	II	III
Normal axis	+	+	+/-
Left axis	+	-	-
Right axis	-	+/-	+



4.1.7. P WAVE

P wave = Atrial depolarization

- **Best seen:** Lead II and V1
- **Deflection:** It is usually upright. It is normally inverted in aVR and occasionally in V1. It may be biphasic in V1 (V1 can be used to assess P wave formed by each atrium).
- **Shape:** Smooth contour
- **Amplitude/ height:**<2.5 mm in limb leads, <1.5 mm in chest leads
- **Duration:**<120 ms (<3 small squares)
- **Axis:** 0-75 degrees

Absent P waves:
Atrial fibrillation, atrial flutter, SA block, nodal rhythm, ventricular rhythm, supraventricular tachycardia, hyperkalemia.

Tall P wave (P-pulmonale): (height >2.5 mV)
Right atrial enlargement

Small P wave:
Atrial rhythm, nodal rhythm

Wide P wave (P-mitrale): (width >0.11 s = 2.5 small squares)
Left atrial enlargement

Inverted P wave:
Normally in V1 and aVR
Incorrectly placed leads, dextrocardia, nodal rhythm with retrograde conduction, low atrial rhythm

Variable P waves:
Wandering pacemaker, multifocal atrial tachycardia

4.1.8. Q WAVE

Q wave = ventricular septal depolarization

- **Best seen:** Usually absent in most leads. Small q wave may be seen in I, II, aVL, V5 and V6. May be seen in lead III during expiration.
- **Deflection:** negative
- **Shape:** sharp
- **Amplitude:**<2 mm. It is 25% or less in amplitude of the following R wave in the same lead.
- **Width:** 1 small square

Pathological Q wave: Depth >2 mm; Width >0.04 seconds (1 small square); should be present in more than one lead; is associated with loss of height of corresponding R wave; should be more than 25% of the following R wave.

4.1.9. R WAVE

R wave = Ventricular depolarization

- **Deflection:** upwards
- **Shape:** sharp
- **Amplitude:** Usually small (<1 mm in V1 and V2)
- **Width:**<0.01 seconds
- **R wave progression:** R wave progressively increases in height from V1 to V6.

Poor R wave progression: It is failure of R wave amplitude to reach >3 mm in lead V3 (There should be no frank Q waves in V1-3).

4.1.10. S WAVE

S wave = Ventricular depolarization

- **Deflection:** downwards
- **S wave progression:** S waves progressively decreases in amplitude from V1 to V6.
- In V3 S and R waves are identical.

4.1.11. QRS COMPLEX

QRS complex: Ventricular depolarization

- **Deflection:** predominantly positive in aVL, V5 and V6.
- **Shape:** sharp
- **Amplitude:** normal height <25 mm
- **Width:**<0.09 ms
- **Low-voltage QRS:** QRS amplitude (R + S) <5 mm in limb leads and <10 mm in all precordial leads.

4.1.12. T WAVE

T wave = Ventricular repolarization

- **Deflection:** Upright in all leads except aVR. May be inverted in V1 and V2.
- **Shape:** Tip of T wave is smooth (rounded)
- **Amplitude:** Normally not more than 5 mm in standard leads and 10 mm in chest leads. It is ¼ the height of corresponding R wave.

Tall symmetrically peaked narrow T waves:
- Hyperkalemia (narrow symmetrical)

Tall asymmetrically peaked broad T waves (hyperacute T waves):
- Early ST elevation MI
- Prinzmetal's angina

Inverted T waves:
- Children, myocardial infarction/ ischemia, bundle branch block, pulmonary embolism, hypertrophic cardiomyopathy, raised intracranial pressure, hypokalemia

Biphasic T waves:
- Ischemia, hypokalemia.

4.1.13. U WAVE

"It is a broad wave after QRS, formed by delayed repolarization of Purkinje fibres OR afterdepolarizations in ventricles."

- **Best seen:** V1 and V2
- **Deflection:** It is usually in the same direction as the T wave.
- **Shape:** Ascending limb is steeper than the descending limb.
- **Height:** Its height is inversely related to the heart rate. Maximum amplitude is 1-2 mm or <25% of the corresponding T wave.

Prominent U wave: (amplitude >1-2 mm or >25% of corresponding T wave)
Bradycardia, severe hypokalemia, hypocalcemia, hypomagnesemia, hypotherma, raised ICP, LVH, hypertrophic cardiomyopathy

Inverted U wave: (highly specific sign of ischemia especially LAD/LM disease)

Coronary artery disease, hypertension, valvular heart disease (aortic and mitral), congenital heart disease, cardiomyopathy, hyperthyroidism

4.1.14. QT INTERVAL

QT interval = electrical depolarization and repolarization of ventricles.

- It is the time between start of QRS complex and the end of T wave.
- Best measured: II and V5-6
- Short QT: <350 ms
- Prolonged QT: >440 ms (in males), >460 ms (in females)

Table 4.2. QT NOMOGRAM

QT NOMOGRAM	Males	Females
Very long QT	>470 ms	>480 ms
Long QT	450 – 470 ms	460 – 480 ms
Long QT possible	390 – 450 ms	400 – 460 ms
Normal QT	360 – 390 ms	370 – 400 ms
Short QT	330 – 360 ms	340 – 370 ms
Very short QT	<330 ms	<340 ms

Causes of prolonged QT:

- Electrolyte disturbances e.g. hypocalcemia, hypokalemia, hypomagnesemia
- Hypothermia
- Myocardial ischemia
- Post-cardiac arrest
- Raised intracranial pressure
- Congenital long QT syndromes
- Drugs
    - Antimicrobials: macrolides, quinolones, doxycycline
    - Antimalarials: chloroquine, hydroxychloroquine, quinine
    - Type IA anti-arrhythmics: quinidine, procainamide, disopyramide
    - Type IC anti-arrhythmics: flecainide, encanide
    - Type III anti-arrhythmics: sotalol, amiodarone
    - Anti-psychotics: chlorpromazine, haloperidol, droperidol, quetiapine, olanzapine, amisulpride, thioridazine
    - Tricyclic antidepressants: amitriptyline, nortriptyline, doxepin, imipramine, desipramine
    - Selective serotonin re-uptake inhibitors: escitalopram, citalopram
    - Antihistamines: diphendramine, loratadine, fexofenadine, terfanadine

4.1.15. ST SEGMENT

It is the segment of the ECG between the end of S wave (J wave) and beginning of T wave. It is the interval between ventricular depolarization and repolarization.

- **Causes of ST elevation:** ST-elevation myocardial infarction, Prinzmetal's angina, pericarditis, benign early repolarization, left bundle branch block, left ventricular hypertrophy, hyperkalemia, ventricular aneurysm, Brugada syndrome, ventricular paced rhythm, raised ICP, Takotsubo cardiomyopathy.
- **Causes of ST depression:** myocardial infarction, posterior wall myocardial infarction (V1 and V2), ventricular hypertrophy with strain pattern, digoxin toxicity.

Causes of st elevation in aVR:

- Left main coronary artery (LMCA) occlusion
- Proximal left anterior descending artery occlusion
- Severe three-vessel disease
- Diffuse sub-endocardial ischemia e.g. following CPR
- Atrio-ventricular re-entrant tachycardia

Table 4.3. CRITERIA FOR DIAGNOSIS OF ST CHANGES

	Males	Females
ST ELEVATION CRITERIA		
V2 and V3	**males ≥40 years:** ≥0.2 mV or 2 mm **males <40 years:** ≥0.25 mV or 2.5 mm	≥0.15 mV
Standard 12 leads (except V2 and V3)	≥0.1 mV	≥0.1 mV
V3R and V4R	**males ≥30 years:** ≥0.05 mV **males <30 years:** ≥0.1 mV	≥0.05 mV
V7-9	≥0.05 mV	≥0.05 mV
ST DEPRESSION CRITERIA		
V2 and V3	≥0.05 mV	≥0.05 mV
Standard 12 leads (except V2 and V3)	≥0.1 mV	≥0.1 mV

Table 4.4. DIFFERENCES IN ST ELEVATION OF MYOCARDIAL INFARCTION AND PERICARDITIS

MYOCARDIAL INFARCTION	PERICARDITIS
Typical chest pain (central chest heaviness but <1% of pains may be pleuritic) Usually convex or horizontal ST elevation (concave ST elevation does not rule out MI) Changes are localized Reciprocal changes seen ST elevation in lead III is greater than lead II PR depression is usually not seen (unless there is atrial infarction in which case it is also localized) ECG changes over time (changes are rapid over hours)	Characteristically pleuritic chest pain is present Concave ST elevation (almost never convex upwards) Changes are usually generalized (may be localized) No reciprocal changes except in aVR and V1 (PR elevation and ST depression) ECG changes slowly progressive No loss of R wave height ECG changes over time (changes are slow over days)

4.1.16. ECG IN MYOCARDIAL INFARCTION

I Cx or Diagonal	aVR	V1 LAD	V4 LAD
II RCA or LCX	aVL Cx or Diagonal	V2 LAD	V5 Cx or Diagonal
III RCA or LCX	aVF RCA or LCX	V3 LAD	V6 Cx or Diagonal

4.1.17. IMPORTANT ECG PATTERNS

LEFT MAIN CORONARY ARTERY SYNDROME:

- ST elevation ≥1 mm in aVR
- ST elevation in aVR ≥ V1
- Generalized ST depression (most prominently in leads I, II, and V4-6) with inverted T waves.
- It is an STEMI equivalent and indicates critical stenosis of the LMCA.

FIRST DIAGONAL BRANCH OF THE LEFT ANTERIOR DESCENDING ARTERY OCCLUSION:

It results in the infarction (STEMI equivalent) of the anterolateral wall of the left ventricle.

- ST elevation in aVL and V2.
- Upright T waves in aVL and V2.
- ST depression and inverted T waves in inferior leads (III and aVF).
- Lack of ST elevation in other precordial leads.

DE WINTER'S T WAVES:

- These are prominent symmetrical tall T waves in precordial leads (V_{1-4}) with an up-sloping ST segment depression >1 mm. There is ST elevation ≥0.5 mm in aVR ± aVL. These may be followed by development of ST elevations in precordial leads.
- It is an anterior STEMI equivalent and indicates proximal LAD occlusion.

WELLEN'S SYNDROME:

These are deeply inverted or biphasic T waves in the presence of following conditions:

- Recent angina
- No pathological Q waves in precordial leads
- Minimal or no ST elevation
- Preserved R wave progression
- Minimal or no cardiac biomarker elevation

It may present as two types:

- Type A: Biphasic T waves (25%)
- Type B: Deeply inverted symmetric T waves (75%)

It frequently indicates impending LAD occlusion and needs cardiologist's review.

POSTERIOR WALL MYOCARDIAL INFARCTION:

Consider posterior wall MI in case of:

- Horizontal ST depression in leads V_{1-3}.
- Prominent, tall and broad R waves in leads V_{1-3}.
- Upright T waves leads V_{1-3}.
- Dominant R wave in V_2.

Record posterior lead ECG V_{7-9} to differentiate between anterior ischemia from posterior wall MI. ST elevation ≥0.5mm in V_{7-9} is diagnostic of posterior wall MI.

CEREBRAL T WAVES/ NEUROGENIC T WAVES:

- Deep symmetric T wave inversions in all leads
- Greatly prolonged QT interval

They may be seen in subarachnoid hemorrhage, intracranial hemorrhage, raised intracranial pressure, ischemic stroke, traumatic brain injury and cerebral metastases.

4.1.18. ECG CHANGES IN DIFFERENT METABOLIC DISORDERS

HYPOKALEMIA:

- Mild – moderate hypokalemia: Flat or inverted T wave, Prominent U wave, ST depression, Prolonged QT
- Severe hypokalemia: Prolonged PR interval, low voltage QRS, wide QRS

HYPERKALEMIA:

- Mild hyperkalemia: Peaked T waves (earliest sign)
- Moderate hyperkalemia: Wide, flat P wave, prolonged PR interval, P wave disappears
- Severe hyperkalemia: Prolonged QRS, bizarre-shaped QRS, high-grade AV block with slow junctional/ ventricular escape rhythms, bundle branch blocks, fascicular blocks, sinus bradycardia, slow atrial fibrillation, sine wave
- Life-threatening hyperkalemia (>9.0 mEq/l): Asystole, ventricular fibrillation, PEA with bizarre, wide complex rhythm.

HYPOCALCEMIA:

- Intermittent prolongation of QT interval, intermittent prolongation of ST segment, T wave is typically unaffected.
- Torsades de pointes, ventricular tachycardia, complete heart block.

HYPERCALCEMIA:

- Mild – moderate: Short Qt interval, short ST segment, wide or flat T waves
- Severe: Osborne waves (J waves), frequent PVC's, ventricular fibrillation, ST segment elevation

HYPONATREMIA:

- Occasionally causes non-ischemic ST elevations in severe cases

HYPOMAGNESEMIA:

- Prolonged QTc, atrial and ventricular ectopics, atrial tachyarrhythmias, torsades de pointes.

HYPERMAGNESEMIA:

- Mild-moderate: Bradycardia, prolonged PR, prolonged QRS, prolonged QT.
- Severe: complete heart block, asystole.

4.2. CONGENITAL HEART DISEASE

⇨ ***Most common congenital heart disease is ventricular septal defect.***
⇨ ***Most common congenital heart disease encountered in adults is atrial septal defect.***

4.2.1. ATRIAL SEPTAL DEFECT (ASD)

"It is an abnormal opening in between the atria."

QUICK FACTS: ATRIAL SEPTAL DEFECT	
Pathology:	**Left-to-right shunt → increased right heart output → pulmonary hypertension**
Presentation:	**Asymptomatic** **Exercise intolerance, exertional dyspnea, fatigue**
Examination:	**Wide fixed splitting of S2, mid-diastolic rumbling murmur** **Signs of pulmonary hypertension and right heart failure**
Diagnosis:	**Trans-esophageal echocardiogram** **Contrast echo or bubble study** **Right heart catheterization**
Treatment:	**Observation; Catheter or surgical repair for ASDs with RV load**

TYPES OF ASDS:

1. Sinus venosus ASD: occurs high up in atrial septum near the opening of superior vena cava.
2. Ostium primum ASD: occur near atrio-ventricular valves. Are common in Down syndrome.
3. Ostium secundum ASD: (most common variety) occur in mid-septum in the area of fossa ovalis.
4. Patent foramen ovale: causes a right to left shunt when foramen ovale fails to close after birth.
5. Coronary sinus ASD: very rare

PATHOPHYSIOLOGY:

- Left-to-right shunt → increased right heart output → pulmonary hypertension.

CLINICAL PRESENTATION:

- Usually asymptomatic (till 30 – 40 years of age), exercise intolerance, exertional dyspnea, fatigue.
- Examination reveals:
  - S1 normal or split
  - Wide fixed splitting of S2
  - Mid-diastolic rumbling murmur along 4th intercostal space
  - Left parasternal heave (if RVH)
  - Palpable pulmonary sound, midsystolic murmur (if pulmonary hypertension)
  - Cyanosis and clubbing (once right to left shunt develops)
- Complications: pulmonary hypertension, shunt reversal (Eisenmenger's disease), right heart failure, atrial fibrillation, stroke (paradoxical emboli from DVT or atrial fibrillation).

INVESTIGATIONS:

- ECG: may show rSr' pattern in right sided leads (RBBB), right axis deviation, right atrial enlargement or right ventricular hypertrophy.
- Chest x-ray: may show increased cardiothoracic ratio, enlarged right atrium and right ventricle, increased pulmonary markings.
- Transesophageal echocardiogram (TEE) is diagnostic.
- Contrast echocardiography
- Bubble study
- Right heart catheterization

MANAGEMENT:

- Most do not require closure.
- Catheter or surgical repair for ASDs with right ventricular overload or Qp/Qs >1.5

4.2.2. VENTRICULAR SEPTAL DEFECT (VSD)

"It is an abnormal opening in between the ventricles."

QUICK FACTS: VENTRICULAR SEPTAL DEFECT	
Pathology:	**Left-to-right shunt causes volume overload of left ventricle**
Presentation:	**Asymptomatic** **Left ventricular failure**
Examination:	**Holosystolic murmur in fourth intercostal space** **Pulmonary hypertension** **Features of left ventricular failure**
Diagnosis:	**Echocardiography with color flow doppler**
Treatment:	**Endocarditis prophylaxis in small VSDs** **Treatment of left ventricular failure** **Surgical repair if complicated**

TYPES:

1. Membranous: occur in the membranous part of ventricular septum. These are usually congenital and occur in children.
2. Muscular: occur in the muscular part of ventricular septum. These are usually acquired and are seen in adults.

It can also be classified as:

1. Type A: doubly committed sub-arterial VSDs lie beneath the pulmonic valve
2. Type B: peri-membranous VSD lie just below the aortic vlave.
3. Type C: inlet or AV-canal type VSD lie posterior to the septal leaflet of the tricuspid valve
4. Type D: muscular VSD

PATHOGENESIS:

- Communication between ventricles → left-to-right shunt → LV volume load, pulmonary hypertension, reduced cardiac output → LV dilation and hypertrophy.

PRESENTATION:

Symptoms:

- Small VSDs: usually asymptomatic.
- Larger VSDs: excessive sweating, fatigue or tachypnea with feeds; growth failure.
- Eisenmenger syndrome (shunt reversal): exertional dyspnea, cyanosis, chest pain, syncope and hemoptysis with exercise.

Signs:

- Left-to-right shunt and murmur severity are inversely related to the size of VSD. Small VSDs produce larger murmurs (maladie de Roger).
- Loud harsh holosystolic murmur in the left third and fourth intercostal spaces along the sternum.
- If pulmonary hypertension present: loud P2, pulmonic regurgitation.
- Complications: heart failure, pulmonary hypertension, shunt reversal (Eisenmenger syndrome), endocarditis, aortic regurgitation.

INVESTIGATIONS:

- Chest x-ray: shows enlarged RV, LA, LV and pulmonary arteries.
- Electrocardiography: signs of LVH or RVH or both.
- Echocardiography with color flow Doppler
- Magnetic resonance angiography
- Cardiac catheterization

TREATMENT:

- Small VSDs: endocarditis prophylaxis (only if previous history of endocarditis), surgical repair if symptomatic.

- Moderate to large VSD: management of heart failure e.g. diuretics, rate-control.
- Surgical repair if elevated pulmonary artery pressure or infective endocarditis.
- Heart-lung transplantation in case of Eisenmenger syndrome.

⇨ ***Ventricular septal defect is the most common congenital heart defect.***

4.2.3. PATENT DUCTUS ARTERIOSUS (PDA)

"Patent ductus arteriosus is a persistent communication between descending thoracic aorta and pulmonary artery (failure of closure of ductus arteriosus)."

QUICK FACTS: PATENT DUCTUS ARTERIOSUS	
Pathology:	**Left-to-right shunt causes volume overload**
Presentation:	**Asymptomatic** **Exercise intolerance**
Examination:	**Continuous machinery murmur** **Features of pulmonary hypertension**
Diagnosis:	**Echocardiography particularly bubble contrast echo is diagnostic.**
Treatment:	**Surgical ligation (if pulmonary hypertension not developed)**

- During fetal life prostaglandins keep the shunt open thus bypassing blood from pulmonary artery to aorta as lungs have not expanded.

PATHOPHYSIOLOGY:
- Large left-to-right shunt → volume overload, pulmonary hypertension, heart failure.

ASSOCIATIONS:
- Congenital rubella syndrome, premature births, high altitude.

SYMPTOMS:
- Asymptomatic, decreased exercise tolerance.
- Infants: tachypnea, sweating, difficulty feeding, inability to gain weight (failure to thrive).

SIGNS:
- L→R shunt: Left ventricular hypertrophy
- Pulmonary hypertension: Loud P2, right ventricular hypertrophy
- Signs of heart failure
- Wide pulse pressure, bounding peripheral pulses
- Continuous (systolic plus diastolic) machinery murmur at left second intercostal space
- Differential clubbing and Cyanosis (lower limbs involved)

COMPLICATIONS:
- Heart failure, shunt reversal (Eisenmenger syndrome)

INVESTIGATIONS:
- Chest x-ray: pulmonary vascular markings, dilated pulmonary artery, increased cardiothoracic ratio.
- Echocardiography: PDA, turbulent flow

TREATMENT:
- Surgical ligation (if no pulmonary hypertension)
- Surgery is contraindicated if pulmonary hypertension or shunt reversal.
- Indomethacin

⇨ ***Prostaglandins E1 is used to keep PDA patent in cases of transposition of great vessels.***
⇨ ***Intake of indomethacin or NSAIDs is associated with early closure of PDA.***

4.2.4. COARCTATION OF AORTA

"It is a narrowing or constriction in aorta leading to obstruction."

QUICK FACTS: COARCTATION OF AORTA	
Pathology:	**Narrowing in aorta causes pressure loading of left ventricle, relative ischemia of distal tissues promotes salt water retention and hypertension**
Presentation:	**Features of peripheral vascular insufficiency**
Examination:	**Radio-femoral delay** **Mid-systolic murmur** **Differential hypertension, clubbing and cyanosis**
Diagnosis:	**Echocardiography, MRI, cardiac catheterization**
Treatment:	**Surgical decompression, percutaneous balloon aortoplasty**

PATHOPHYSIOLOGY:

- Aortic obstruction → increased left ventricular afterload → left ventricular failure

SYMPTOMS:

- Headache, cold extremities, exercise-induced claudication, leg fatigue

SIGNS:

- Differential hypertension (upper limb BP > lower limb BP)
- Differential hypertrophy (upper limb more developed than lower limb)
- Differential clubbing and cyanosis
- Mid-systolic murmur (heard best over back)
- Radio-femoral delay

COMPLICATIONS:

- Left ventricular failure, secondary hypertension, infective endocarditis, rupture of cerebral aneurysms, aortic dissection.

INVESTIGATIONS:

- ECG: Features of LVH
- Chest x-ray:
- Notching of ribs
- 3 sign: indented aorta at site of coarctation

TREATMENT:

- Surgical decompression
- Percutaneous balloon aortoplasty

4.2.5. TETRALOGY OF FALLOT (TOF)

"It is a group of cardiac abnormalities secondary to defects in formation of infundibular septum."

QUICK FACTS: TETRALOGY OF FALLOT	
Pathology:	**Right-to-left shunt (cyanotic)** **Four cardinal features: pulmonic stenosis, VSD, over-riding aorta, right ventricular hypertrophy**
Presentation:	**Tet spells, squatting to improve symptoms, failure to thrive**
Examination:	**Cyanosis, clubbing, crescendo-decrescendo murmur**
Diagnosis:	**Echocardiography and right heart catheterization**
Treatment:	**Surgical correction**

FOUR CARDINAL FEATURES:

- Infundibular pulmonary stenosis or RV outflow tract obstruction (RVOTO)
- Ventricular septal defect (septal)
- Over-riding aorta (dextro-position)
- Right ventricular hypertrophy

PATHOPHYSIOLOGY:

- R → L shunt at the VSD worsened by RVOTO (predominant)
- L → R shunt if less RVOTO

SYMPTOMS:

- Tet spells (episodes of bluish skin during crying or feeding)
- Squatting after exertion
- Difficulty with feeding, failure to thrive, exertional dyspnea.

SIGNS:

- Growth retardation
- Cyanosis
- Finger clubbing
- Crescendo-decrescendo systolic ejection murmur (best at left upper sternal border)

INVESTIGATIONS:

- Echocardiography (diagnostic)
- ECG: enlarged RA and RV
- Chest x-ray: boot-shaped heart
- Right heart catheterization

TREATMENT:

- Surgical correction

⇨ ***The greater the RV outflow obstruction, the more the cyanosis and softer the murmur.***

⇨ ***Most common symptom of TOF is cyanosis.***

⇨ ***Fallot's Pentad = 4 features of TOF + atrial septal defect.***

4.3. VALVULAR HEART DISEASE

Table 4.5. CAUSES OF DIFFERENT MURMURS

	Left sided	Right sided	Others
Systolic murmurs	MR (pansystolic) AS (ejection systolic) HOCM (ejection systolic)	TR (pansystolic) PS (ejection systolic)	VSD (pansystolic) MVP (mid- to late-systolic) Coarctation of aorta
Diastolic murmurs	MS (mid-diastolic) AR	TS PR	ASD (mid-diastolic) Austin Flint (in AR) Left atrial myxoma (mid-diastolic) Carey Coombs (with rheumatic fever) Graham Steell (with PR or pulmonary hypertension)

Table 4.6. CARDIAC MANEUVERS (DYNAMIC AUSCULTATION)

Valsalva maneuver	Decreases venous return
Standing	Decreases venous return
Squatting	Increases venous return. Also increases peripheral resistance.
Leg raise	Increases venous return.
Hand grip	Increases peripheral resistance/ afterload and decreases cardiac emptying.

Table 4.7. EFFECT OF DIFFERENT MANEUVERS ON MURMUR INTENSITY

	Valsalva	Standing	Squatting	Leg raise	Hand-grip
Mitral stenosis	Decreases	Decreases	Increases	Increases	-
Mitral regurgitation	Decreases	Decreases	Increases	Increases	Increases
Aortic stenosis	Decreases/ same	Decreases	Increases	Increases	Decreases/ same
Aortic regurgitation	Decreases	Decreases	Increases	Increases	Increases
Tricuspid regurgitation	Decreases				
Mitral valve prolapse	Increases	-	Decreases	Decreases	Decreases
Hypertrophic obstructive cardiomyopathy	Increases	Increases	Decreases	Decreases	Decreases
Ventricular septal defect			Increases		
Atrial septal defect	Decreases				

⇨ ***All named murmurs are diastolic in origin e.g. Graham-Steell, Austin-Flint, Carey Coombs.***

⇨ ***Right-sided murmurs increase on inspiration (Carvallo sign) while left-sided murmurs increase on expiration.***

⇨ ***All left sided murmurs increase with maneuvers that increase venous return (squatting, leg-raise test), except mitral valve prolapse.***

⇨ ***Valsalva maneuver is used to differentiate murmurs of hypertrophic obstructive cardiomyopathy and aortic stenosis.***

⇨ ***Amyl nitrate inhalation decreases afterload and hence decreases murmur of mitral regurgitation.***

4.3.1. MITRAL STENOSIS (MS)

"Mitral stenosis is narrowing of mitral orifice resulting in elevation of pressure gradients across it."

QUICK FACTS: MITRAL STENOSIS	
Pathology:	**Narrowed mitral valve → elevated LA pressure → pulmonary venous hypertension → pulmonary edema → eventual right heart failure in long-run**
Presentation:	**Dyspnea, palpitations (May worsen after any activity that increases heart rate)**
Examination:	**Loud S1, opening snap after A2, mid-diastolic rumbling murmur Right heart failure**
Diagnosis:	**Echocardiography**
Treatment:	**Balloon valvuloplasty Mitral valve repair**

CAUSES:

- After rheumatic fever; Congenital; calcific degeneration

PATHOPHYSIOLOGY:

- Obstruction → reduced left ventricular filling →elevated left atrial pressure → elevated pulmonary venous pressure, pulmonary congestion and reduced cardiac output

GRADING OF SEVERITY OF MITRAL STENOSIS:

- Mild:
  - Mitral valve area: >1.5 cm2
  - Mean pressure gradient across mitral valve: <5 mmHg
  - Pulmonary artery systolic pressure: <30 mmHg
- Moderate:
  - Mitral valve area: 1 – 1.5 cm2
  - Mean pressure gradient across mitral valve: 5 – 10 mmHg
  - Pulmonary artery systolic pressure: 30 – 50 mmHg
- Severe:
  - Mitral valve area: <1 cm2
  - Mean pressure gradient across mitral valve: >10 mmHg
  - Pulmonary artery systolic pressure: >50 mmHg

SYMPTOMS:

- Exertional dyspnea, orthopnea, PND, palpitations, chest pain, hemoptysis.
- Exertion, anemia, fever, tachycardia, pregnancy, intercourse and excitement are common triggers. These may lead to pulmonary edema.

PHYSCIAL EXAMINATION:

- Stenosis: Palpable or loud S1; opening snap after A2; mid-diastolic rumbling murmur with presystolic accentuation (in sinus rhythm).
- Pulmonary hypertension: Loud P2
- Right heart failure: right ventricular heave, raised jugular venous pressure, ascites, peripheral edema, hepatomegaly.

COMPLICATIONS:

- Hemoptysis, pulmonary hypertension, right heart failure, pulmonary embolism, atrial fibrillation, pneumonia, systemic emboli leading to gangrene, cerebrovascular accident, etc., infective endocarditis

INVESTIGATIONS:

- **ECG:** Left atrial enlargement; atrial fibrillation;if pulmonary hypertension develops then right axis deviation and right ventricular hypertrophy.

- **Chest x-ray:** Left atrial or right ventricular enlargement, straightened left heart border, Kerley B lines, prominent pulmonary arteries
- **Echocardiogram:** Inadequate separation and calcification of mitral valve leaflets; narrow fish mouth-shaped opening; enlarged left atrium.
- **Cardiac catheterization:** helps to establish severity of MS
- **Doppler:** Narrow valve area, increased trans-mitral valve gradient, pulmonary hypertension.

TREATMENT:

- Prophylaxis for acute rheumatic fever: PENICILLIN V PO or BENZATHINE PENICILLIN G
- Salt restriction
- Oral diuretics
- Rate control of atrial fibrillation: beta blockers, rate-limiting calcium channel blockers, digitalis.
- Anticoagulation in case of atrial fibrillation: Warfarin
- Surgical treatment: percutaneous balloon valvuloplasty; mitral valvotomy, valve replacement if very severe.

⇨ ***Duration of murmur is proportional to the severity of disease.***

⇨ ***Duration of gap between opening snap and A2 is inversely related to severity of disease.***

⇨ ***Severe mitral stenosis is characterized by a valve area <1cm^2, mean trans-mitral gradient >10 mmHg and pulmonary artery systolic pressure >50 mmHg.***

⇨ ***Causes of mid-diastolic murmurs: Mitral stenosis, Tricuspid stenosis, Atrial septal defect, Left atrial myxoma, Austin-Flint murmur (heard in AR), Carey-Coomb's murmur (heard in acute rheumatic fever).***

4.3.2. MITRAL REGURGITATION (MR)

QUICK FACTS: MITRAL REGURGITATION	
Pathology:	**Regurgitation through mitral valve → elevated LA pressure → pulmonary venous hypertension → pulmonary edema → eventual right heart failure in long-run**
Presentation:	**Dyspnea, palpitations (May worsen after any activity that increases heart rate)**
Examination:	**Displaced apex beat, soft S1 Pansystolic murmur radiates to axilla or back**
Diagnosis:	**S3 gallop**
Treatment:	**Reduce afterload Mitral valve replacement or repair**

CAUSES:

- Mitral valve prolapse
- Rheumatic heart disease
- Ischemic heart disease with papillary muscle dysfunction
- Ruptured chordae tendinae
- LV dilatation due to any cause
- Mitral annular calcification
- Hypertrophic cardiomyopathy
- Infective endocarditis
- Congenital

PATHOPHYSIOLOGY:

- Acute MR: rise in left atrial pressure → pulmonary edema
- Chronic MR: portion of stroke volume leaks back into left atrium →gradual rise in left atrial pressure → dilated LA and LV → pulmonary hypertension

PRESENTATION:

Symptoms:

- Dyspnea on exertion, orthopnea, PND, palpitations

Physical examination:

- Displacement of apex beat laterally
- Soft S1
- Widened S2
- Loud P2
- S3 gallop
- Pan-systolic murmur at apex area which radiates to axilla or back
- Atrial fibrillation

Complications:

- Left ventricular failure

INVESTIGATIONS:

- ECG:Features of left atrial enlargement and LVH
- Echocardiogram:Mitral regurgitation, dilated LA and LV, decreased LV function

TREATMENT:

- Salt restriction
- Diuretics for congestion
- Reduce afterload: nifedipine, hydralazine + nitrates, ACEIs
- Anti-coagulation (if atrial fibrillation)
- Surgical: mitral valve repair or replacement

4.3.3. AORTIC STENOSIS (AS)

QUICK FACTS: AORTIC STENOSIS	
Pathology:	**Narrowed aortic valve → pressure loading of left ventricle → LV dilatation → failure of cardiac output to increase upon effort → effort angina**
Presentation:	**Angina, syncope** **Symptoms of heart failure**
Examination:	**Well-sustained apical heave** **Slow rising pulse** **Harsh ejection systolic crescendo-decrescendo murmur → radiates to carotids**
Diagnosis:	**Echocardiography**
Treatment:	**Asymptomatic: no treatment** **Symptomatic: treat heart failure, surgical valve repair, TAVI, balloon valvuloplasty (palliative)**

CAUSES:

- Calcified valve in elderly (most common cause in elderly)
- Calcified bicuspid aortic valve (most common cause in young)
- Rheumatic fever
- Congenital

PATHOPHYSIOLOGY:

- LV outflow obstruction → left ventricular hypertrophy → dilated LV → also develops MR
- As LV obstruction increases → cardiac output fails to increase → angina

GRADING OF SEVERITY OF AORTIC STENOSIS:

- Normal:
  - Aortic valve area: 3.0 – 4.0 cm2
  - Mean pressure gradient across aortic valve: <5 mmHg
  - Aortic jet velocity: ≤2.0 m/s
- Mild:
  - Aortic valve area: >1.5 cm2
  - Mean pressure gradient across aortic valve: <25 mmHg
  - Aortic jet velocity: <3.0 m/s

- Moderate:
  - Aortic valve area: 1.0 – 1.5 cm2
  - Mean pressure gradient across aortic valve: 25 – 40 mmHg
  - Aortic jet velocity: 3.0 – 4.0 m/s
- Severe:
  - Aortic valve area: <1.0 cm2
  - Mean pressure gradient across aortic valve: >40 mmHg
  - Aortic jet velocity: >4.0 m/s

PRESENTATION:

Symptoms:

- Angina
- Syncope
- Symptoms of heart failure e.g. exertional dyspnea, orthopnea, PND

Signs:

- Well-sustained apical heave
- Precordial thrill
- Soft S2; S4 (marker of severity)
- Harsh ejection-systolic crescendo-decrescendo murmur heard best in second right intercostal space and radiates to carotids.
- Pulsus parvus et tardus (diminished and delayed) slow-rising pulse

Complications:

- Left ventricular failure

INVESTIGATIONS:

- ECG: Signs of LVH and LAE, ST-T changes (left ventricular strain pattern)
- Echocardiogram: Diagnostic investigation: shows LVH, thickened immobile aortic valve and dilated aortic root.

TREATMENT:

- Asymptomatic: no treatment
- Symptomatic:
  - Avoid strenuous exercise.
  - Treat heart failure.
  - Surgical aortic valve replacement
  - Transcatheter aortic valve implantation (TAVI)
  - Balloon aortic valvotomy (palliative)

4.3.4. AORTIC REGURGITATION/ INSUFFICIENCY (AR)

QUICK FACTS: AORTIC REGURGITATION	
Pathology:	**Regurgitation through aortic valve → increased LV end-diastolic volume → elevated left atrial pressure → heart failure**
Presentation:	**Dyspnea on exertion, orthopnea, PND**
Examination:	**Signs of aortic regurgitation: wide pulse pressure, collapsing pulse, de Musset sign, Corrigan's sign, Muller sign, lighthouse sign, etc.** **Diastolic decrescendo murmur** **Austin Flint murmur (apical diastolic murmur)**
Diagnosis:	**Echocardiogram**
Treatment:	**Asymptomatic chronic AR: treat heart failure** **Acute AR or symptomatic chronic AR: surgical valve replacement**

CAUSES:

- Primary AR
  - Infective endocarditis

    - Rheumatic fever
    - Trauma
    - Bicuspid aortic valve
    - Aortic dissection
    - Drugs e.g. fenfluramine
    - Balloon valvulotomy
- Secondary AR
    - Age (myxomatous degeneration)
    - Hypertension
    - Aortitis
    - Aortic dissection
    - Trauma

PATHOPHYSIOLOGY:

- Regurgitant fluid → increased left ventricular end-diastolic volume → LV dilation and hypertrophy → elevated left sided pressures → left ventricular failure

PRESENTATION:

Symptoms:

- Dysnea on exertion, orthopnea, PND, palpitations, chest pain; shock (in acute AR)

Signs:

- Precordial examination:
    - Laterally displaced apex beat.
    - Diastolic decrescendo murmur heard best at left sternal border. Decreases on hand-grip maneuver.
    - Austin-Flint murmur: apical diastolic murmur
    - Soft S1 and S2
    - S3 and S4 heard
- Peripheral signs:
    - De Musset's sign: visible head bobbing with each heart beat
    - Corrigan's sign (dancing carotids): visible pulsations of supraclavicular area and carotids
    - Pulsus bisferiens (double systolic impulse): seen in combined AR and AS
    - Becker's sign: pulsations of retinal arterioles
    - Landolfi's sign: systolic contraction and diastolic dilatation of pupils
    - Ashrafian sign: pulsatile pseudo-proptosis
    - Muller's sign: visible systolic pulsations of uvula
    - Light-house sign: visible flushing and emptying of face with each heartbeat
    - Wide pulse pressure: due to raised systolic blood pressure and reduced diastolic blood pressure
    - Corrigan's pulse or water-hammer pulse = abrupt arterial pressure decrease in late systole and diastole.
    - Mayne's sign: decrease in diastolic blood pressure of 15 mmHg when arm is elevated above head.
    - Palmar click: visible flushing of palm with systole
    - Quincke's sign: capillary pulsations in distal nail-bed
    - Pistol-shot femorals (Traube's sign): loud sound over femoral artery when stethoscope lightly placed over it.
    - Duroziez's sign: to and fro bruit with gradual compression of femoral artery
    - Hill's sign: Popliteal systolic blood pressure > brachial systolic blood pressure
    - Rosenbach's sign: hepatic pulsations
    - Gerhardt's sign (Sailer's sign): pulsations of spleen when it is enlarged
    - Shelly's sign: pulsations of cervix
    - Lincoln's sign: excessive popliteal pulsations
    - Sherman's sign: easily localized and pulsatile dorsalis pedis in elderly patient

Complications:

- Left heart failure, infective endocarditis (with dental or genitourinary procedures)

INVESTIGATIONS:

- ECG: Signs of LVH

- Echocardiogram: Shows regurgitant flow, dilated aortic root and LV size.
- Cardiac catheterization: Assesses severity of AR

TREATMENT:

- For asymptomatic patients: salt restriction, diuretics, vasodilators, digoxin, drugs to reduce afterload (ACE inhibitors or arterial vaodilators), limit physical activity.
- For symptomatic patients and for those with severe LVF: surgical aortic valve replacement
- For acute AR: emergency valve replacement
- Endocarditis prophylaxis is need in case of dental and GI/genitourinary procedures.

4.3.5. TRICUSPID STENOSIS (TS)

- Tricuspid stenosis is rare and mostly caused by rheumatic heart disease. It usually occurs in association with other valvular abnormalities. It presents as right heart failure.

4.3.6. TRICUSPID REGURGITATION (TR)

QUICK FACTS: TRICUSPID REGURGITATION	
Pathology:	**Regurgitation through tricuspid valve → right heart failure**
Presentation:	**Asymptomatic**
Examination:	**Lower limb swelling, abdominal distension** **Raised JVP (pulsatile), tender pulsatile hepatomegaly, ascites, edema** **Pansystolic murmur**
Diagnosis:	**Echocardiogram**
Treatment:	**Mild to moderate: treat underlying cause, diuretics** **Severe TR without pulmonary hypertension: surgical repair** **Severe TR with pulmonary hypertension: conservative treatment**

CAUSES:

- Left ventricular failure
- Right ventricular infarction
- Inferior wall myocardial infarction
- Cor pulmonale secondary to pulmonary hypertension
- Infective endocarditis (occurs in iv drug abusers)
- Rheumatic heart disease
- Carcinoid syndrome
- SLE
- Myxomatous valve degeneration
- Epstein's anomaly (congenital downward displacement of tricuspid valve into tight ventricle)

PATHOPHYSIOLOGY:

- Regurgitation of blood into right atrium → right heart failure

PRESENTATION:

Symptoms:

- Usually asymptomatic
- Lower limb swelling
- Abdominal distension
- Right hypochondrial pain

Signs:

- Features of right heart failure: raised JVP (with prominent V waves and rapid y descent), ascites, peripheral edema, hepatomegaly (characteristically pulsatile liver)
- Right ventricular heave
- Pan-systolic murmur of blowing nature, heard best at left lower sternal border. Murmur increases with inspiration and decreases with expiration or Valsalva maneuver.

- Irregularly irregular pulse due to atrial fibrillation.

Complications:

- Right heart failure

INVESTIGATIONS:

- ECG: Signs of RAE and RVH
- Echocardiogram: Demonstrates TR, state of valves and pulmonary artery pressures

TREATMENT:

- Treat underlying cause
- Diuretics
- For severe TR in absence of pulmonary hypertension: surgical treatment
- For severe TR in case of pulmonary hypertension: conservative treatment

⇨ ***Most common cause of tricuspid regurgitation is left ventricular failure.***

4.3.7. MITRAL VALVE PROLAPSE (MVP)

Aka Click-Murmur syndrome, Barlow's syndrome, floppy valve syndrome

"It is the presence of excessive mitral leaflet tissue due to myxomatous degeneration of mitral valve leaflets and/or chordae tendinae."

QUICK FACTS: MITRAL VALVE PROLAPSE	
Pathology:	**Regurgitation through tricuspid valve → right heart failure**
	Asymptomatic
Presentation:	**Lower limb swelling, abdominal distension**
Examination:	**Raised JVP (pulsatile), tender pulsatile hepatomegaly, ascites, edema**
	Pansystolic murmur
Diagnosis:	**Echocardiogram**
Treatment:	**Mild to moderate: treat underlying cause, diuretics**
	Severe TR without pulmonary hypertension: surgical repair
	Severe TR with pulmonary hypertension: conservative treatment

CAUSES:

- Myxomatous degeneration of valve leaflets
- Association with genetic connective tissue orders: Marfan's syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, Loeys-Dietz syndrome.
- Association with autoimmune thyroid disorders

PATHOPHYSIOLOGY:

- Prolapse of leaflet tissue towards left atrium in systole → regurgitation of blood into left atrium → produces click and murmur

SYMPTOMS:

- Asymptomatic (mostly)
- Symptoms of autonomic dysfunction: anxiety, panic attacks, palpitations, atypical chest pain.
- Symptoms of progression: fatigue, dyspnea, exercise intolerance, orthopnea, PND
- Transient ischemic attacks

SIGNS:

- Mid-systolic or late-systolic click: intensity increases by standing and Valsalva maneuver and decreases by squatting.
- Mid-to-late systolic murmur: intensity increases by standing and Valsalva maneuver and decreases by squatting.

COMPLICATIONS:

- Complications are very rare and include mitral regurgitation, left heart failure, endocarditis, TIAs, arrhythmias and sudden death.

INVESTIGATIONS:

- ECG: usually normal
- Echo: demonstrates MVP (anterior and posterior mitral leaflets bulge posteriorly in systole). TEE is superior.
- Cardiac MRI

TREATMENT:

- Asymptomatic: no treatment, follow with echocardiogram every 3 – 5 years
- Symptomatic: beta-blockers for chest pain. Avoid stimulants like coffee, chocolate, alcohol, etc.
- Asymptomatic patients with severe MR and LVEF 30-60%: surgery

⇨ ***Mitral valve prolapse is the most common valvular abnormality in developed countries.***

4.3.8. ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

"Acute rheumatic fever is a systemic immunological process caused by cross-reacting antibodies to joints and heart after a group A streptococcal infection (pharyngitis)."
"Rheumatic heart disease is presence of chronic valvular abnormalities which occur as a complication of acute rheumatic fever."

QUICK FACTS: ACUTE RHEUMATIC FEVER	
Pathology:	**Infection with rheumatogenic group A streptococci → cross-reacting antibodies → inflammation at multiple sites**
Presentation:	**Polyarthritis**
Examination:	**Carditis** **Erythema marginatum** **Sydenham chorea** **Subcutaneous nodules**
Diagnosis:	**Streptococcal antibodies, throat cultures, clinical presentation (Duckett-Jones criteria)**
Treatment:	**Echocardiography (for chronic disease)** **Antibiotics** **High-dose NSAIDs** **Secondary prophylaxis**

- Acute rheumatic fever occurs 2 – 3 weeks after the infection with rheumatogenic group A streptococci, mostly in children and young adults. Attacks typically resolve in 12 weeks. Subcutaneous nodules and Sydenham's chorea are late presentation.
- Rheumatic heart disease is progressive valve fibrosis which develops in patients with carditis and acute rheumatic fever. Mitral and aortic valves are characteristically involved.

PATHOPHYSIOLOGY:

- Acute rheumatic fever: Infection with rheumatogenic group A streptococci → antibodies against microbes cross-react with host antigens → inflammation at target sites
- Rheumatic heart disease: results from permanent damage to heart valves or muscle due to inflammation and fibrosis → stenosis, regurgitation or heart failure

PRESENTATION:

- Pharyngitis: sore-throat occurs weeks before features of rheumatic fever. Intake of appropriate antibiotics decreases incidence of rheumatic fever.
- Polyarthritis: symmetrical, usually involves large joints, joint involvement spreads from one joint to another (migratory) and may overlap. Tenosynovitis may occur in adults
- Carditis: presents as heart failure
- Erythema marginatum: non-pruritic painless erythematous lesions on trunk
- Sydenham chorea: usually occurs in children due to autoantibodies against ganglioside

- Subcutaneous nodules:
- Other features: fever, abdominal pain, joint pain, malaise

INVESTIGATIONS:

- For acute rheumatic fever:
  - CRP and ESR
  - Rising streptococcal antibody titer (e.g. ASO, anti-DNAse B, antistreptokinase, antihyalurondase, anti-DNAase)
  - Throat culture for group A beta-hemolytic streptococci
- For chronic rheumatic heart disease:
  - Echocardiography

Table 4.8. DIAGNOSTIC CRITERIA FOR ACUTE RHEUMATIC FEVER (DUCKETT JONES CRITERIA)
Major criteria: 1. Migratory polyarthritis (earliest feature) 2. Erythema marginatum 3. Cardiac involvement (pancarditis, pericarditis, myocarditis, endocarditis) 4. Subcutaneous nodules 5. Sydenham's Chorea (St Vitus dance) **Minor criteria:** 1. Fever ≥38.5°C 2. Increased ESR and/or increased CRP 3. Polyarthralgias 4. Prolonged PR interval 5. Previous history of rheumatic fever **Evidence of preceding group A streptococcal infection** 1. Elevated or rising anti-streptolysin O titer (ASOT) or other streptococcal antibody 2. Positive throat culture 3. Rapid antigen test for group A streptococcus 4. Recent scarlet fever
Two major criteria **OR** **One major and two minor** **PLUS** **Evidence of preceding group A streptococcal infection**

TREATMENT:

- For acute rheumatic fever:
  - Antibiotics for pharyngitis to prevent rheumatic fever e.g. penicillin, erythromycin
  - NSAIDs e.g. high dose aspirin
  - Bed rest
  - Steroids are controversial in carditis
  - Secondary prophylaxis for recurrent rheumatic fever
- For rheumatic heart disease:
  - Management of valvular pathology
  - Antibiotic prophylaxis for patients undergoing procedures

Table 4.9. SECONDARY PROPHYLAXIS FOR PREVENTION OF RHEUMATIC HEART DISEASE	
Patient features	**Duration of prophylaxis**
Patient with proven carditis	For 5 years after the last attack or 18 years of age (whichever is longer)
Patients with carditis	For 10 years after the last attack or 25 years of age (whichever is longer)
More severe valvular disease	Lifelong
Valvular surgery	Lifelong

⇨ ***Most common valvular abnormality in rheumatic heart disease is mitral stenosis.***

4.3.9. INFECTIVE ENDOCARDITIS

"Infective endocarditis is an infection of endocardium which includes native or prosthetic heart valves, septal defects or mural endocardium."

QUICK FACTS: INFECTIVE ENDOCARDITIS	
Pathology:	**Infection of endocardium → heart failure, embolic phenomena, vasculitic phenomena, metastatic infections**
Presentation:	**Fever, malaise, weight loss, headache**
Examination:	**New or changing murmurs**
Diagnosis:	**Petechiae, splinter hemorrhages, Janeway lesions, Osler lesions, Roth spots, clubbing** **Echocardiogram (transthoracic or transoesophageal)**
Treatment:	**Blood cultures** **Native valve: penicillin,, ceftriaxone, gentamicin** **Prosthetic valve: penicillin G, ceftriaxone, nafcillin, nafcillin** **Surgical intervention**

CAUSATIVE ORGANISMS:

- Staphylococcus aureus (most common)
- Streptococcus viridans
- Group D streptococci
- Coagulase negative staphylococci
- Enterococci
- Aerobic gram negative bacilli including Pseudomonas
- HACEK organisms:
    - Hemophilus species e.g. H. parainfluenza, H. aphrophilus (now Aggregatibacter aphrophilus), H. paraphrophilus.
    - Actinobacillus actinomycetemcomitans (now Aggregatibacter actinomycetemcomitans)
    - Cardiobacterium hominis
    - Eikenella corrodens
    - Kingella species
- Bartonella species
- Listeria species
- Corynebacterium diphtheria
- Brucella
- Coxiella burnetii
- Fungi

TYPES:

IE can be divided on the basis of duration into acute and sub-acute IE.

- Acute:
    - Occurs on normal valves.
    - Mostly caused by S. aureus.
    - Death occurs in <6 weeks if untreated.
- Sub-acute:
    - Occurs on damaged valves.
    - Mostly caused by less virulent organisms e.g. S. viridans, enterococci, other bacteria, fungi.
    - Course is prolonged >6 weeks.
    - Symptoms are subtle and less well-defined.

It can also be divided on the basis of valve type and iv drug use:

- Native valve endocarditis
- Prosthetic valve endocarditis
    - Early-onset (within 2 months):

- Late-onset (after 2 months):
- Endocarditis in intravenous drug abusers

Table 4.10. MODIFIED DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS
Major clinical criteria in blood: • Two blood cultures positive for typical organisms e.g. Streptococcus viridans, Streptococcus bovis, HACEK group, Staphylococcus aureus, or community-acquired enterococci in the absence of a primary focus. • Single positive blood culture for Coxiella burnetii or anti-phase 1 IgG antibody titer ≥1:800. • Micro-organisms consistent with IE from persistently positive blood cultures defined as follows: at least two positive blood cultures drawn >12 hours apart Or all 3 or a majority of ≥4 separate blood cultures (with first and last samples drawn at least 1 hour apart). **Major clinical criteria in echocardiogram:** • Evidence of an oscillating intra-cardiac mass on a valve or on supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation. • Myocardial abscess. • New partial dehiscence of a prosthetic valve. • New-onset valvular regurgitation (worsening or changing or pre-existing murmur not sufficient). **Pathological criteria:** • Micro-organisms in culture or histological examination of a vegetation, an embolized vegetation or an intra-cardiac abscess specimen; or pathological lesions; vegetation or intra-cardiac abscess confirmed by histological examination showing active endocarditis.
Minor criteria: • Predisposing heart condition or intravenous drug abuse. • Fever of 38°C (100.4°F) or higher. • Vascular phenomenon, major arterial emboli, septic pulmonary infarcts, mycotic aneurysms,intra-cranial hemorrhage, conjunctival hemorrhages, and Janeway lesions. • Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor. • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above (excludes single positive cultures for coagulase negative staphylococci and organisms that do not cause endocarditis) or serological evidence of active infection with organism consistent with IE.
Definitive endocarditis: two major clinical criteria OR one major and three minor clinical criteria OR five minor clinical criteria OR pathological criteria **Possible endocarditis:** one major and one minor criteria OR three minor criteria **Rejected endocarditis:** firm alternative diagnosis OR resolution of IE syndrome with antibiotic therapy for ≤4 days OR no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 days OR does not meet criteria for possible IE as above

PRESENTATION:

- Fever: usually low-grade, may be associated with chills
- Malaise, weight loss, headache
- Classical signs:
  - Petechiae: non-specific
  - Splinter hemorrhages: linear dark-red lesions in nail-beds
  - Janeway lesions: non-tender macules on palms and soles
  - Osler nodes: tender subcutaneous nodules in pulp of fingers
  - Roth spots: retinal hemorrhages with clear centers
  - Clubbing
  - New or changing murmurs
- Features of complications e.g. neurologic defects, signs of heart failure, pericarditis, pleuritis, renal emboli, glomerulonephritis
- Splenomegaly

COMPLICATIONS:

- Congestive heart failure
- Valvular dysfunction, rupture or perforation
- Cardiac abscesses
- Embolic showering in different organs e.g. brain (stroke or intra-cerebral hemorrhage), kidneys (renal failure)
- Metastatic infections e.g. abscesses or osteomyelitis (usually occurs in lumbar vertebrae)
- Mycotic aneurysms

INVESTIGATIONS:

- Trans-esophageal echocardiogram (first line test in patients with prosthetic valves, or those with possible IE, or complicated IE)

- Trans-thoracic echocardiogram (can be performed as first line in remaining patients)
- Blood cultures: 3 – 5 sets from different sites within 60 – 90 minutes. Thereafter send two sets of blood cultures after every 24 – 48 hours till clearance of organism.
- Chest x-ray: features of heart failure or pulmonary infiltrates
- ECG: may show AV blocks in case of ring abscesses

TREATMENT:

- After cultures start with empiric antibiotics penicillin (or vancomycin) and aminoglycoside then switch according to cultures.
    - Native valve endocarditis with penicillin-susceptible S. viridans and S. bovis:
        - PENICILLIN G 2 – 3 million units iv every 4 hours for 4 weeks OR
        - PENICILLIN G with GENTAMICIN 1 mg/kg iv every 8 hours
        - CEFTRIAXONE 2 g IV or IM once daily for 4 weeks
        - CEFTRIAXONE with GENTAMICIN 1 mg/kg iv every 8 hours for 2 weeks
        - VANCOMYCIN 30 mg/kg in 24 hours in 2 divided doses for 4 weeks in penicillin or ceftriaxone allergy
    - Native valve endocarditis with penicillin-resistant S. viridans and S. bovis:
        - PENICILLIN G for 4 weeks and GENTAMICIN for 2 weeks
        - CEFTRIAXONE for 4 weeks and GENTAMICIN for 2 weeks
        - VANCOMYCIN for 4 weeks in penicillin or ceftriaxone allergy
    - Prosthetic valve endocarditis with penicillin sensitive S. viridans and S. bovis:
        - PENICILLIN G for 6 weeks with or without GENTAMICIN for 2 weeks
        - CEFTRIAXONE for 6 weeks with or without GENTAMICIN for 2 weeks
    - Native valve endocarditis with staphylococci:
        - NAFCILLIN or OXACILLIN 12 g/24 hours in 4 – 6 divided doses for 6 weeks with optional GENTAMICIN for 3 – 5 days
        - CEFAZOLIN 6g/24 hours in 3 divided doses for 6 weeks with optional GENTAMICIN for 3 -5 days
        - VANCOMYCIN for 6 weeks in case of oxacillin-resistant strains
    - Prosthetic valve endocarditis with staphylococci:
        - NAFCILLIN or OXACILLIN 12 g/24 hours in 6 divided doses for ≥6 weeks with RIFAMPICIN 900 mg/24 hours IV or PO in 3 divided doses for ≥6 weeks with GENTAMICIN for 2 weeks
        - VANCOMYCIN for ≥6 weeks with RIFAMPIN for ≥6 weeks with GENTAMICIN for 2 weeks in oxacillin-resistant strains
    - OTHER ORGANISMS: require specific therapy
- Anticoagulation is not beneficial.
- Surgical intervention in case of heart failure unresponsive to medical therapy, acute aortic or mitral insufficiency, valve perforation or rupture or large or unresponsive vegetations.

PROPHYLAXIS:

- Endocarditis prophylaxis should be taken before dental and pulmonary procedures in high-risk cardiac conditions: prosthetic heart valves, previous infective endocarditis, unrepaired cyanotic congenital heart disease, repaired congenital heart disease with prostheses, repaired congenital heart disease with residual heart disease and cardiac transplant patients with valvulopathy.
- Prophylactic antibiotics include AMOXICILLIN, CLINDAMYCIN, CEPHALEXIN, AZITHROMYCIN, CLARITHROMYCIN, AMPICILLIN or CEFAZOLIN.

⇨ ***Staphylococcus aureus is the most common cause of infective endocarditis.***

⇨ ***Staphylococcus aureus is the most common cause of infective endocarditis in injection drug users and early-onset prosthetic valve endocarditis.***

⇨ ***Streptococcus viridans is the most common cause of late-onset prosthetic valve endocarditis and sub-acute endocarditis.***

4.4. ISCHEMIC HEART DISEASE

"It is a spectrum of disorders related to myocardial ischemia i.e. mismatch between cardiac demand and vascular supply."

Causes of ischemic heart disease:

- Atherosclerosis (most common), vasculitis, anemia, stress

Presentations of ischemic heart disease:

1. Stable angina
2. Unstable angina
3. Prinzmetal's angina
4. Non ST-elevation myocardial infarction
5. ST-elevation myocardial infarction
6. Cardiac syndrome X (microvascular angina)
7. Sudden cardiac death
8. Heart failure
9. Arrhythmias

Risk factors for atherosclerotic heart disease:

Major risk factors:

1. Hypertension: defined as per new ACC/ AHA guidelines.
2. Diabetes: defined as in chapter on endocrinology.
3. Dyslipidemia: defined as cholesterol level >, LDL level >130 mg/dl and HDL level <40 mg/dl.
4. Cigarette smoking or tobacco use:
5. Family history of premature coronary artery disease: defined as onset of coronary artery disease at age <45 years in father or first-degree male relatives or age <55 years in mother or first-degree female relatives OR definite myocardial infarction or sudden cardiac death at age <55 years in father or first-degree male relatives or age <65 years in mother or first-degree female relatives.
6. Age: defined as age >45 years in males and >55 years in females (>45 years in females with early menopause without estrogen replacement).

Significant risk factors:

1. Chronic renal insufficiency particularly those on hemodialysis
2. Rheumatoid arthritis, SLE, etc.

Minor risk factors:

1. Obesity
2. Sedentary life-style
3. Stress or type A personality
4. Excessive alcoholism
5. Passive tobacco smoking

Novel risk factors:

1. Raised CRP levels
2. Raised homocysteine levels
3. Prior mycoplasma infection

4.4.1. STABLE ANGINA

"It is angina due to a fixed obstructive atherosclerotic lesion which increases oxygen demand as compared to resting coronary flow."

QUICK FACTS: ISCHEMIC HEART DISEASE – STABLE ANGINA	
Pathology:	**Fixed coronary artery lesion → insufficient coronary blood flow during exertion → symptoms of ischemia**
Presentation:	**Exertional chest pain, dyspnea, sweating**
Examination:	**None**
Diagnosis:	**Resting ECG or echocardiogram: usually normal** **Stress testing** **Coronary angiography**
Treatment:	**Anti-platelet**

	Rate control: beta-blockers or rate-limiting calcium channel blockers **Nitrates: sublingually on SOS basis + regular nitrates** **Statins** **Modify risk factors** **Coronary angioplasty (medically refractory)**

PRESENTATION:

- Pain in chest, jaw, shoulder, back or arm which lasts less than 20 minutes, is precipitated by exertion and is relieved by rest or sublingual nitrates. Pain may be absent in elderly and patients who are immunosuppressed or have advanced diabetes or neuropathy. In such cases dyspnea is present (angina equivalent).

Table 4.11. DIAMOND'S CLASSIFICATION OF CHEST DISCOMFORT
1. Chest with characteristic quality and duration 2. Pain worsened by exertion or emotional stress 3. Relieved by rest or nitroglycerine
Typical angina = all 3 of above Atypical angina = 2 of above Non-cardiac chest pain = 1 of the above

INVESTIGATIONS:

- *ECG:* may be normal at rest, shows ST-T changes during angina episode or after exertion.
- *Stress test:* involves stressing the heart for evidence of ischemia or symptoms. Stress can be in the form of exercise on a treadmill or pharmacological stressors (using iv adenosine, dipyridamole or dobutamine).
    - *Stress ECG:* ECG is recorded before, during and after stress. Exercise induced ischemia may present as reproduction of symptoms or ST depressions. Test may also detect severity of heart failure as well as exercise-induced arrhythmias.
    - *Stress echocardiography:* Echocardiography is performed before and after stress. It detects areas of dyskinesia (ischemic areas with possible reversibility) or akinesia (ischemic areas with possible irreversibility). It is superior to ECG and also detects LV function and valvular abnormalities.
    - *Myocardial perfusion imaging:* it studies the differential uptake of a radio-isotope (e.g. thallium 20) in viable and non-viable myocardial cells.
- *Holter monitoring:* it is ambulatory ECG monitoring of patient and is useful for detecting silent ischemia as well as arrhythmias, heart rate variations and pacemaker/ICD function.
- *Cardiac catheterization:* It is a definite test for detecting coronary artery lesions. Anatomical lesions must be correlated with functional lesions on ECG or stress test. Percutaneous coronary intervention can also be performed.

Table 4.12. CANADIAN CARDIOVASCULAR SCALE (CCS) FUNCTIONAL CLASSIFICATION OF STABLE ANGINA	
Class I	Angina during strenuous or prolonged physical activity
Class II	Angina on moderate exertion
Class III	Pain on mild exertion
Class IV	Pain on minimal exertion or at rest

TREATMENT:

- General measures: quit smoking; control hypertension, diabetes and dyslipidemia; weight loss, exercise ; dietary precautions (lowintake of cholesterol and saturated fats)
- Anti-platelets: Aspirin. If intolerant to aspirin, then use CLOPIDOGREL, PRASUGREL or TICAGRELOR.
- Anti-anginals:
    - Nitrates (on-demand short-acting sublingual nitrates or long-acting oral nitrates)
    - Beta-blockers e.g. ATENOLOL, METOPROLOL, NEBIVULOL
    - Calcium channel blockers (only if beta-blockers are contraindicated).

- Novel anti-anginals (can be considered after optimization of classical anti-anginals if symptoms are persistent): Ivabradine, Ranolazine, Nicorandil,
- ACE inhibitors: if concomitant congestive heart failure
- Diuretics: if concomitant congestive heart failure
- Percutaneous coronary intervention/ coronary angioplasty: in patients with severe medically-refractory angina, decreased EF, and three-vessel/left main disease.

⇨ ***Coronary arteriography/angiography is the most accurate test for detecting coronary artery disease.***

4.4.2. UNSTABLE ANGINA

"It is angina due to acutely worsening atherosclerotic plaque either due to thrombosis, hemorrhage or plaque rupture."

QUICK FACTS: ISCHEMIC HEART DISEASE – UNSTABLE ANGINA	
Pathology:	**Rupture of atherosclerotic plaque, thrombosis or hemorrhage → increased coronary obstruction → worsened angina (but no tissue death)**
Presentation:	**New chest pain or worsened chest pain**
Examination:	**No direct signs**
Diagnosis:	**Resting ECG** **Troponins (to rule out MI)** **Echocardiography (wall motion abnormalities)** **Stress testing (after unstable phase)** **Coronary angiography (in high risk patients)**
Treatment:	**Dual antiplatelets** **Statins** **Nitrates** **Anticoagulants** **Rate-control: beta blockers or rate-limiting calcium channel blockers** **Coronary angioplasty (medically refractory)**

Table 4.13. BRAUNWALD's CLASSIFICATION OF UNSTABLE ANGINA

		Secondary angina (develops in presence of an extra-cardiac condition that increases myocardial ischemia)	Primary unstable angina (develops in absence of extra-cardiac condition)	Post-infarction unstable angina (develops within 2 weeks of acute myocardial infarction)
		A	B	C
New-onset exertional angina (new onset of severe angina or accelerated angina; no rest pain)	I	I A	I B	I C
Sub-acute angina at rest (angina at rest within past month but not within preceding 48 hours)	II	II A	II B	II C
Acute angina at rest (angina at rest within past 48 hours)	III	III A	III B (Can be either Trop-negative or Trop-positive)	III C

There is reduced resting coronary blood flow and unchanged myocardial oxygen demand.
The instability of lesion can progressive to non-ST elevation or ST elevation myocardial infarction.
It includes all angina patients who have following features:

- New onset angina
- Newly worsening angina
- Angina at rest
- Angina within one month of an acute myocardial infarction

INVESTIGATIONS:

- ECG: ST-T changes except those of ST elevation, ST elevation equivalents or pathological Q waves.
- Cardiac markers: cardiac markers and troponins are not raised in contrast to other ACS.
- Coronary angiography: may be considered
- Stress test: should be performed after stabilization

TREATMENT:

Treatment is same as myocardial infarction except for thrombolysis and hurry of revascularization.

- Oxygen (if hypoxia)
- Aspirin
- Clopidogrel
- Beta-blockers
- Anti-coagulation: unfractionated heparin or low-molecular-weight heparin (LMWH)
- Nitrates
- Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban)
- Morphine
- Diuretics (for congestion)
- Percutaneous coronary revascularization: conservative versus invasive management based on risk scores. Following patients should be considered for early invasive management:
    - Patients with high risk (as assessed by TIMI, GRACE and HEART scores)
    - Patients initially chosen for conservative treatment whose symptoms or ischemic changes in ECG persist after 48 hours.
    - Patients with hemodynamic instability
    - Patients with ventricular arrhythmias
    - Patients with mechanical complications e.g. new mitral regurgitation, new septal defects.
- General measures: quit smoking; control hypertension, diabetes and dyslipidemia; weight loss, exercise ; dietary precautions (lowintake of cholesterol and saturated fats)

Table 4.14. THROMBOLYSIS IN MYOCARDIAL INFARCTION (TIMI) RISK SCORE FOR UNSTABLE ANGINA/ NON ST ELEVATION MYOCARDIAL INFARCTION

Features	POINTS
Age ≥65 years	1
3 or more risk factors for coronary artery disease	1
Known CAD with >50% stenosis	1
Aspirin use in past 7 days	1
Severe angina in preceding 24 hours	1
Elevated cardiac enzymes	1
ST deviation greater than 0.5 mm	1

⇨ ***Acute coronary syndromes (ACS) include unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction***

⇨ ***Non-ST elevation acute coronary syndromes (NSTE-ACS) include unstable angina and non-ST elevation myocardial infarction.***

4.4.3. PRINZMETAL'S/ VARIANT/ VASOSPASTIC ANGINA

"It is defined as a transient coronary vasospasm usually caused by a fixed atherosclerotic lesion but sometimes in the absence of coronary lesion."

QUICK FACTS: ISCHEMIC HEART DISEASE – PRINZMETAL'S ANGINA	
Pathology:	**Coronary artery vasospasm → symptoms of ischemia**
Presentation:	**Angina**
Examination:	**No direct signs**
Diagnosis:	**Coronary angiography and intra-coronary injection of ergonovine**
Treatment:	**Calcium channel blocekrs** **Nitrates**

	Statins

PRESENTATION:

- Episodes of angina at rest usually at night
- Associated with ventricular arrhythmias which can be lethal

INVESTIGATIONS:

- ECG: Transient ST elevation
- Troponins/ cardiac markers: are not raised or minimally raised
- Coronary angiography: displays coronary spasm on intra-coronary injection of ergonovine.

MANAGEMENT:

- Life-style modifications: quit smoking, dietary precautions
- Oral calcium channel blockers and nitrates relieve spasm.
- Statins

4.4.4. MYOCARDIAL INFARCTION

"It is death and necrosis of myocardial tissue due to sudden occlusion of blood supply."

QUICK FACTS: ISCHEMIC HEART DISEASE – MYOCARDIAL INFARCTION	
Pathology:	**Plaque rupture leading to thrombosis (rarely other causes e.g. thrombosis, dissection, critically reduced blood flow) → myocardial tissue death**
Presentation:	**Severe chest pain, dyspnea, sweating, nausea, vomiting, feeling of impending doom**
Examination:	**Sweating, S3, signs of shock**
Diagnosis:	**ECG: ST elevations in STEMI, ST depressions/ T inversions in NSTEMI** **Troponins and cardiac markers** **Echocardiography**
Treatment:	**General: loading doses of aspirin, second antiplatelet, high dose statins, oxygen if hypoxemic, anticoagulants, nitrates, pain relief** **STEMI: revascularization using PCI or thrombolytics**

TYPES OF MYOCARDIAL INFARCTION (THIRD UNIVERSAL DEFINITION OF MI):

- Type 1: it is due to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus.
- Type 2: it is due to ischemic imbalance e.g. vasospasm, endothelial dysfunction.
- Type 3: it includes sudden cardiac deaths accompanied by new ECG changes or new LBBB but without cardiac markers.
- Type 4: infarction in the setting of PCI
- Type 5: infarction in the setting of CABG

SYMPTOMS:

- Chest pain: intense sub-sternal chest pain described as "heaviness" or "crushing". Pain may be radiating to neck (usually in LM disease), jaw, arms (usually left side) and back. It is similar to angina but usually lasts longer than 20 minutes and is more severe in nature and does not relieve with nitroglycerine. Pain may occasionally occur solely in epigastrium (typically inferior wall MI), arm or neck. Pain is unlikely to be ischemic if it has following characterisitcs (however these should not be the sole basis for ruling out ischemic pain):
    - Very short duration (few seconds)
    - Very long duration (hours)
    - Pleuritic nature
    - Pain with tenderness
    - Pain related to movement of upper limb
- Silent MI: Certain elderly, diabetics, immunocompromised and post-operative patients do not experience chest pain or may experience other symptoms like breathlessness, palpitations, ghabrahat, etc.
- Breathlessness

- Weakness
- Fatigue
- Anxiety
- Fear of impending doom or death
- Nausea or vomiting
- Sweating
- Syncope/ collapse
- Sudden death (usually due to ventricular fibrillation)

SIGNS:

- Signs of sympathetic activation: pallor, sweating, tachycardia
- Signs of vagal activation: vomiting, bradycardia
- Signs of impaired myocardial function: hypotension, oliguria, cold peripheries, narrow pulse pressure, raised JVP, third heart sound, quiet S1, diffuse apical impulse, crepts in lungs.
- Signs of tissue damage: low-grade fever
- Signs of complications: mitral regurgitation, pericarditis, pericardial effusion

ECG:

It is usually suggestive in 96% of cases.

- Trans-mural infarction: Peaked tall T waves → St elevation → Q wave formation. Other features may include poor R wave progression or persistent St elevations (usually indicate akinetic segment or aneurysm).
- Sub-endocardial infarction: T inversions, St depressions

CARDIAC MARKERS:

- Troponins: these are the most sensitive and specific diagnostic tests for NSTEMI to differentiate it from unstable angina. Although highly elevated in ST elevation, waiting for troponin levels is not recommended in STEMI.
    - Troponins are repeated at 6 – 8 hours and a rising trend is evidence of myocardial infarction.
    - False-positive causes: renal failure, intramuscular injection, rhabdomyolysis, etc.
- Highly sensitive troponins (hs-cTn): these are highly sensitive markers for earlier detection of MI. Tests are performed at presentation, at 3 hours and at 6 hours.
    - If baseline hscTn ≤upper range limit then a >50% of upper range limit elevation at 3-hour or 6-hour is diagnostic.
    - If baseline hscTn >upper range limit then a >20% of initial value at 3-hour or 6-hour is diagnostic.
    - Accelerated protocol: hscTn is repeated at 0, 1 or 2 hours to rule out myocardial infarction.
- CK-MB: it is less commonly used however can be of value in diagnosing re-infarction because of shorter half-life.
- CK-MB to CK ratio:
    - Elevated CK-MB and a CK-MB to total CK ratio >2.5 (or 3) = cardiac damage
    - Elevated CK and a CK-MB to total CK ratio <2.5 = muscle damage

Table 4.15. TIMINGS OF ONSET, PEAK AND DURATION OF DIFFERENT CARDIAC MARKERS

	Onset	Peak	Duration
Troponin I	3 – 8 hours	24 – 48 hours	3 – 5 days
Troponin T	3 – 8 hours	72 – 100 hours	5 – 10 days
CK (total) and CK-MB	3 – 12 hours	18 – 24 hours	36 – 48 hours
LDH	6 – 12 hours	24 – 48 hours	6 – 8 days (5 – 10 days)
Myoglobin	1 – 4 hours	6 – 7 hours	24 hours
AST (SGOT)	6 – 12 hours	24 – 48 hours	4 – 6 days

1. Non ST segment elevation myocardial infarction: these are sub-endocardial infarcts and do not involve the entire thickness of the myocardial wall.
2. ST segment elevation myocardial infarction: these are trans-mural infarcts which involve full thickness of wall.

TREATMENT:

- Ensure cardiovascular stability:
- Administer oxygen: administer oxygen if patient having hypoxia (oxygen saturation <90%) however try to taper within 6 hours.
- *Anti-platelets:*
    - *Aspirin:* given as 150 – 300 mg (or 162 – 325 mg). It inhibits thromboxane A2 induced platelet activation.
    - *P2Y12 receptor inhibitors:* these inhibit P2Y12 receptor to inhibit ADP-induced platelet aggregation. These include CLOPIDOGREL (300 – 600 mg), PRASUGREL (60 mg) and TICAGRELOR (180 mg). Combination with aspirin is superior to aspirin or any of these alone, in preventing major adverse cardiovascular events.
    - *Glycoprotein IIb/IIIa inhibitors:* these block GP IIb/IIIa receptors to prevent cross-linking of platelets. These include TIROFIBAN, EPTIFIBATIDE and ABCIXIMAB. These can be added to UFH with reduction in dose especially for PCI.
- *Beta-blockers:* reduce myocardial oxygen demand, infarct size, cardiac remodeling and mortality. These should be used within 24 hours unless bradycardia, shock or heart failure are present. Non-dihydropyridine calcium channel blockers e.g. VERAPAMIL and DILTIAZEM can be used in patients with contraindications to beta-blockers, however these have no mortality benefit.
- *ACE inhibitors:* initiate in acute MI within 24 – 48 hours and titrate dose upwards. These prevent cardiac remodeling and reduce mortality especially in anterior wall MI, EF<40% or with pulmonary edema. These should be avoided in acute renal failure, hyperkalemia, bilateral renal artery stenosis and shock. Angiotensin receptor blockers can be used is patients who do not tolerate ACE inhibitors.
- *Aldosterone antagonists:* Include SPIRONOLACTONE and EPLERENONE. These are used after MI in diabetics or those with EF<30% to reduce mortality.
- *Statins:* High dose early statins stabilize plaques, decrease vascular inflammation, decrease major adverse cardiovascular events and reduce mortality. A fasting lipid profile should be performed within 24 hours.
- *Nitrates:* These include GTN and ISORSOBIDE MONONITRATE. These cause arterio- and veno-dilation and coronary vasodilation. These reduce preload and myocardial oxygen demand and improve coronary blood flow. Initially given sublingually however may be switched to iv infusion if repeatedly required.
- *Morphine/ analgesia:* for pain relief .
- *Anti-coagulation:* These include UNFRACTIONATED HEPARIN (UFH), ENOXAPARIN, BIVALIRUDIN and FONDAPARINUX. Heparin is given for 48 hours or till the end of PCI. Others can be given up to discharge.
- *Reperfusion therapy:* It should be considered for all STEMI patients who present within 12 hours.
    - *Pharmacological revascularization/ thrombolytics:* These are chosen if primary PCI cannot be performed at the hospital and the time for transfer to a PCI-capable hospital would take more than 120 mintues. These can be given up to 12 hours after chest pain in patients with ST elevation of at least 1 mm in two or more contiguous leads or those with new LBBB.
        - Non-specific thrombolytics: streptokinase
        - Clot-specific thrombolytics: ALTEPLASE, RETEPLASE, TENECTEPLASE.
    - *Interventional revascularization:*
        - Primary percutaneous coronary intervention should be done ideally within 30 minutes of arrival in hospital but can be considered up to 12 hours. It can also be considered in 12 – 24 hours period if patients have ongoing clinical or ECG evidence of ischemia.
        - *CABG:* should be considered in patients with mechanical complications leading to cardiogenic shock. Intra-aortic balloon pump counterpulsation can be used as a bridging device if pharmacological therapy fails.
- *Cardiac rehabilitation:* exercise-based programs are recommended to improve survival.
- *Maintenance therapy:*
    - Aspirin: 75 mg (or 81 mg) should be given indefinitely
    - P2Y12 inhibitors: should be given for one year in all patients who undergo PCI with a stent. Doses are CLOPIDOGREL (75 mg once daily), PRASUGREL (10 mg once daily) and TICAGRELOR (90 mg twice daily).

- Other maintenance drugs include beta-blockers (or CCBs), ACE inhibitors (or ARBs), aldosterone antagonists, statins and anti-anginals.
- Anticoagulation with oral drugs should be continued in patients with high-risk atrial fibrillation or those with LV mural thrombi.
- General measures: quit smoking, control of risk factors like diabetes, hypertension and dyslipidemia, eat healthy diet.

⇨ ***Most common cause of myocardial infarction is by rupture of atheromatous plaque with sudden thrombosis.***

4.4.5. COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

1) Arrhythmic complications:

a. *Premature ventricular contractions:* need no treatment. Should be kept under observation.
b. *Ventricular tachycardia:*
    i. If hemodynamically unstable should be cardioverted.
    ii. If hemodynamically: anti-arrhythmics e.g. amiodarone
c. *Accelerated idioventricular rhythm:* needs observation only
d. *Ventricular fibrillation:* immediated defibrillation
e. *Atrial fibrillation:* pharmacological or electrical cardioversion. Rate control or anti-arrhythmics if recurrent. Anticoagulation especially if high risk for stroke.
f. *Paroxysmal supraventricular tachycardia:* rate control agents or anti-arrhythmics
g. *Sinus tachycardia:* treat underlying cause and control rate with beta-blockers.

2) Ischemic complications:

a. Post-infarction angina: treated with anti-anginals or revascularization.
b. Re-infarction: treated with revascularization.
c. Extension of infarction: treated with revascularization.

3) Mechanical complications:

h. *Heart failure:* it occurs as a result of large infarct size, right ventricular infarct, mechanical complications or effects of drugs like beta-blockers. IABP may be inserted to support LV functions. Vasodilators and ACE inhibitors are added to reduce afterload. Diuretics are used to relieve congestion. Dopamine or dobutamine may be considered in some patients. Emergency PCI or surgical revascularization should be done.
i. *Free wall rupture:* it presents as sudden onset of chest pain on straining or coughing. Echocardiography or Swan-Ganz catheter may be used for diagnosis. Emergency pericardiocentesis may be considered. Surgery is definitive treatment.
j. *Rupture of inter-ventricular septum:* presents as rapid recurrence of angina, shock and pulmonary edema. Echocardiograph y should be performed for diagnosis and emergent surgical repair should be done.
k. *Papillary muscle rupture:* leads to acute mitral regurgitation → shock, pulmonary edema. It is diagnosed with echocardiography. Treatment is to reduce afterload with vasodilator therapy or intra-aortic balloon pump. Emergency surgery should be considered.
l. *Ventricular pseudo-aneurysm:* it is caused by a contained free wall rupture. As there is risk of rupture therefore surgery is recommended.
m. *Ventricular aneurysm:* In case of heart failure, vasodilators and ACE inhibitors are added. Anticoagulation is done in case of mural thrombi. LV reconstructive surgery is done for patients with refractory heart failure and arrhythmias. NSAIDs and steroids with acute MI are associated with aneurysm formation.

4) Embolic complications:

a. Cerebral infarcts
b. Digital gangrene
c. Mesenteric embolization

5) Inflammatory complications:

a. Acute pericarditis: may occur in patients who do not undergo revascularization. It is treated with aspirin. NSAIDs and steroids should not be used as they increase incidence of aneurysm formation.
b. Dressler's syndrome (post-myocardial infarction syndrome): it is an immune-mediated syndrome which occurs weeks to months after MI. Patients develop fever, malaise, pericarditis, leukocytosis and pleuritis. First-line treatment is aspirin. Ibuprofen can be used as second line.

4.5. HEART FAILURE

""Heart failure is a condition in which there is any structural or functional abnormality of the heart which causes failure of heart pump resulting in inadequate perfusion of peripheral tissues."*

QUICK FACTS: HEART FAILURE	
Pathology:	**Failure of heart to pump or relax**
Presentation:	**Dyspnea, orthopnea, PND, edema, exercise intolerance**
Examination:	**Tachycardia, hypotension, tachypnea, reduced pulse pressure, S3, diffuse apex beat, pulmonary rales, raised JVP, bilateral pleural effusion**
Diagnosis:	
Treatment:	**Salt water restriction** **ACEI or ARBs or ARNIs (nitrate + hydralazine combo if contraindicated)** **For rate control: beta blockers, ivabradine** **For congestion: diuretics** **For refractory heart failure: MRA, digoxin, CRT, LVAD, cardiac transplantation** **For prevention of arrhythmias: ICD**

It is divided as follows:

1. Left heart failure:
    a. Heart failure due to left ventricular systolic dysfunction (LVSD) i.e. heart failure with reduced ejection fraction (HFrEF) or systolic heart failure
    b. Heart failure with preserved ejection fraction (HFpEF) i.e. heart failure with preserved ejection fraction or diastolic heart failure i.e. EF ≥50% (previously ≥40%).
    c. European Society of Cardiology has introduced a third term for HF with EF ranging from 40 – 49 %. It is known as HFmrEF (HF with mid-range EF).
2. Right heart failure

Table 4.16. CAUSES OF LEFT AND RIGHT VENTRICULAR FAILURE

CAUSES OF LEFT VENTRICULAR FAILURE	CAUSES OF RIGHT VENTRICULAR FAILURE
Ischemic heart disease e.g. left ventricular infarction	Secondary to left ventricular failure
Hypertension	Valvular heart disease (MS, PR, PS)
Valvular heart disease (AS, MR, AR)	Pulmonary hypertension
Cardiomyopathy	Right ventricular infarcts
Myocarditis	Long-standing pulmonary disease (cor pulmonale)
Congenital heart defects	Chronic thromboembolic pulmonary embolism
	Bacterial endocarditis (right-sided)

FACTORS THAT EXACERBATE HEART FAILURE:

- Non-compliance with medicine
- Excessive salt and water intake
- Ischemia/ infarction (e.g. myocardial ischemia, MI, pulmonary embolism)
- Uncontrolled hypertension
- Arrhythmias e.g. atrial fibrillation deprives ventricle of atrial kick
- Anemia
- Pregnancy
- Thyrotoxicosis
- Myocarditis
- Infective endocarditis
- Drugs e.g. verapamil

SYMPTOMS:

- LV Failure (symptoms due to low cardiac output and pulmonary venous congestion):
    - Exertional dyspnea, Orthopnea, Paroxysmal nocturnal dyspnea, cough (worsens on lying), nocturia, fatigue, exercise intolerance, keeps more than one pillow under head or keeps head elevated during sleep, Cheyne-Stokes respiration
- RV Failure (symptoms due to fluid retention):

- Lower limb swelling, right upper quadrant pain (due to hepatic congestion), abdominal distension, nausea or anorexia (from gut edema)

Table 4.17. CAUSES OF HEART FAILURE	
CAUSES OF SYSTOLIC HEART FAILURE	CAUSES OF DIASTOLIC HEART FAILURE
Ischemic heart disease Hypertension → cardiomyopathy Valvular heart disease Myocarditis Alcoholism Radiation Hemochromatosis Thyroid disease	Hypertension → hypertrophy Valvular diseases e.g. AS, MS, AR Restrictive cardiomyopathy Constrictive pericarditis

Table 4.18. NYHA CLASSIFICATION OF HEART FAILURE	
I	Asymptomatic
II	Symptomatic with moderate exertion
III	Symptomatic with mil exertion
IV	Symptomatic at rest

Table 4.19. ACC/AHA STAGES OF HEART FAILURE	
A	Pre-heart failure: patient has family history of heart failure or has one or more risk factors for developing heart failure e.g. diabetes, hypertension, ischemic heart disease, history of rheumatic fever, etc.
B	Patients with demonstrable heart failure who are asymptomatic
C	Patients with symptomatic and objective heart failure
D	Patients have advanced symptoms that do not benefit from treatment

SIGNS:

- LV Failure:
  - Tachycardia, hypotension, tachypnea, reduced pulse pressure, S3, soft S1, pulmonary rales, gallop rhythm, cold extremities and sweating (due to increased sympathetic activity), pulmonary rales, bilateral pleural effusion, enlarged diffuse apex beat
- RV Failure:
  - Elevated JVP, edema, tender hepatomegaly, ascites, S3, left parasternal heave, central and peripheral cyanosis.

INVESTIGATIONS:

- Anemia, raised red cell distribution width
- Other tests: urea, creatinine, TSH
- Chest x-ray:
  - May show increased cardiothoracic ratio, Kerley lines, interstitial markings and pleural effusion.
- Echocardiography
  - First investigation of choice
- BNP and N-terminal pro BNP (help to differentiate dyspnea due to cardiac failure from non-cardiac causes and give prognosis)
- Troponins
- ECG: usually non-specific.
- Radionuclide ventriculography e.g. technetium-99m scan: in cases where echocardiogram interpretation is difficult.
- Cardiac catheterization
- Stress testing

MANAGEMENT OF HFREF:

- General measures:
  - Restrict salt intake (ideally <2 g/day)
  - Fluid restriction
  - Weight loss
  - Stop smoking and alcoholism
  - Exercise: moderate intensity aerobic physical activity of 30 minutes at least 3 times a week

    - Monitor weight daily
    - N-3 polyunsaturated fatty acid supplementation
    - Treat underlying risk factors e.g. hypertension, diabetes, ischemic heart disease.
    - Avoid NSAIDs, decongestants, licorice
    - Annual influenza vaccine
    - Single pneumococcal vaccine
- Diuretics
    - These are given in case of volume overload.
    - Do not improve mortality but provide symptomatic relief.
    - Include loop diuretic (FUROSEMIDE) and thiazide diuretic (HYDROCHLOROTHIAZIDE).
- ACE inhibitors
    - Start in all patients with LVEF <40% (whether symptomatic or not)
    - Start ACE inhibitors in low dose and titrate up to maximal tolerated dose.
    - These confer mortality benefit.
    - Include CAPTOPRIL, ENALAPRIL, RAMIPRIL, LISINOPRIL, TRANDOLAPRIL.
- Angiotensin receptor blockers
    - Started in patients who cannot tolerate ACEIs.
    - Include CANDESARTAN, LOSARTAN and VALSARTAN.
- Angiotensin receptor- Neprilysin inhibitor (ARNI)
    - Substituted in place of ACEIs in patients who remain symptomatic despite tolerating maximal dose of ACEI.
    - Currently only one drug: SACUBITRIL-VALSARTAN
- Beta blockers
    - Start with low doses in stable heart failure.
    - Beta-blockers with proven mortality benefit include METOPROLOL SUCCINATE (not tartarate), CARVEDILOL, BISOPROLOL, ? NEBIVULOL
- Non-dihydropyridine calcium channel blockers:
    - Unsafe in HFrEF.
- If-channel inhibitors:
    - Indicated in symptomatic patients with EF ≤35%, in sinus rhythm and a resting heart rate ≥70 beats per minute who are unable to tolerate a maximal dose of beta-blockers or have contraindications for beta-blockers.
    - Currently only one drug: IVABRADINE
- Aldosterone antagonists or mineralocorticoid receptor antagonists (MRA):
    - Include SPIRONOLACTONE and EPLERENONE.
    - SPIRONOLACTONE confers mortality benefit in symptomatic patients with NYHA III or NYHA IV heart failure or EF ≤35%.
    - EPLERENONE has less side-effects but is currently non-superior to SPIRONOLACTONE.
    - EPLERENONE is used as an alternative to SPIRONOLACTONE in case of side-effects.
- Digitalis
    - Used in case of severe heart failure, EF<40%, or severe atrial fibrillation.
    - No benefit in terms of mortality but reduces hospitalization rates and symptoms.
- Oral hydralazine and nitrate
    - Are used in patients who cannot tolerate ACEIs.
- Oral anti-coagulants:
    - No beneficial role.
    - It should only be used in patients with atrial fibrillation.
- Statins: no beneficial role.
- Implantable cardioverter-defibrillator
    - It is indicated in patients with EF<35% who continue to have NYHA II to III symptoms 40 days after MI.
- Biventricular pacemaker:
    - It is indicated in above –mentioned patients who also have wide QRS.

MANAGEMENT OF DIASTOLIC DYSFUNCTION:

- Beta-blockers

- Diuretics (for congestion)
- ACEIs/ ARBs: unclear role
    - Candesartan may reduce hospitalizations.
- Digoxin: may reduce hospitalizations
- Spironolactone: may reduce hospitalizations
- None of the above drugs confer a mortality advantage in HFpEF or HFmrEF except may be NEBIVULOL. (ESC 2016).

⇨ ***The most frequent cause of systolic heart failure is ischemic heart disease.***

⇨ ***The most frequent cause of diastolic heart failure is left ventricular hypertrophy usually due to long-standing hypertension.***

4.6. ACUTE DECOMPENSATED HEART FAILURE

Aka cardiogenic pulmonary edema

"It is a life-threatening condition of acute failure of heart pump."

QUICK FACTS: ACUTE DECOMPENSATED HEART FAILURE	
Pathology:	**Sudden increased pulmonary pressure → increased pulmonary congestion → pulmonary edema**
Presentation:	**Acute dyspnea, orthopnea, PND, cough**
Examination:	**Tachypnea, chest crepts, S3, JVD**
Diagnosis:	**Clinical diagnosis** **Chest x-ray** **BNP**
Treatment:	**Oxygen** **Nitrates, diuretics, morphine, dobutamine, phosphodiesterase inhibitors** **NIV, IV**

CAUSES:

- Acute myocardial infarction
- LVF exacerbation due to any cause
- Valvular regurgitation (particularly acute ones e.g. MR, AR)
- Ventricular septal defect
- Severe myocardial ischemia
- Infective endocarditis
- Arrhythmias
- Hypertensive crisis
- Cardiomyopathy

PATHOPHYSIOLOGY:

- Sudden increased LA pressure → increased pulmonary congestion → pulmonary edema

PRESENTATION:

- Symptoms: acute dyspnea (more on lying down), orthopnea, paroxysmal nocturnal dyspnea, cough (particularly on lying down), frothy pink sputum, sweating
- Signs: tachypnea (rapid shallow breathing), crepts in chest, S3 gallop, jugular venous distension

INVESTIGATIONS:

- Chest x-ray
    - Pulmonary venous congestion
    - Upper lobe venous diversion
    - Kerley lines
    - Increased cardiothoracic ratio
    - Pleural effusion (usually bilateral, sometimes right sided)
    - Bilateral pulmonary opacities
    - Bat-wing sign (bilateral peri-hilar pulmonary opacities)
- Arterial blood gases

    - Demonstrate hypoxia or acidosis.
- Swan-Ganz catheterization
    - Increased pulmonary capillary wedge pressure ≥25 mmHg
- BNP levels
    - Elevated BNP is sensitive but not specific.
    - A normal BNP almost rules out cardiogenic pulmonary edema.
- Electrocardiography: can show ischemia or arrhythmia

MANAGEMENT:

- Oxygen (keep saturation >90%)
- Keep head end propped up.
- Loop diuretics: FUROSEMIDE, BUMETANIDE, ETHACRYNIC ACID
    - FUROSEMIDE usually given as 1 mg/kg IV bolus. It acts as diuretic as well as venodilator.
    - Reduce preload.
    - Dose should be sufficient to produce an output of 1 – 2 liters in one hour otherwise it should be doubled.
- Morphine
    - Act as pulmonary and systemic venodilator to alter hemodynamics.
    - Given as 2 – 4 mg IV or SC or IM and may be repeated every 15 minutes.
    - It should be given with an anti-emetic.
- NITROGLYCERINE as sublingual or oral spray or Intravenous infusion.
- If above measures are not effective then give CPAP therapy of 8 – 10 cm H2O or enough to keep oxygen saturation >90%. BiPAP if there is respiratory acidosis from exhaustion.
- DOBUTAMINE
    - It is the inotrope of choice.
- Phosphodiesterase inhibitors: INAMRINONE or MILRINONE
- NESIRITIDE (ANP analogue):
    - Role is unclear. May decrease dyspnea.
- If impending respiratory failure or decreased consciousness then intubate and keep on high PEEP.
- Treat the cause which decompensated heart failure e.g. arrhythmia, infarction, ischemia.
- Consider need for intra-aortic balloon pump (IABP).

4.7. CARDIOMYOPATHIES AND MYOCARDITIS

"Cardiomyopathies are conditions of cardiac dysfunction due to disease of cardiac muscle."

4.7.1. DILATED CARDIOMYOPATHY

"It is a cardiac systolic dysfunction due to symmetrical dilatation of the ventricles (chamber enlargement with normal thickness)".

QUICK FACTS: DILATED CARDIOMYOPATHY	
Pathology:	**Systolic dysfunction**
Presentation:	**Heart failure, functional murmurs, arrhythmias**
Diagnosis:	**Echocardiograpm, ECG, cardiac MRI, endomyocardial biopsy, cardiac catheterization**
Treatment:	**Management of heart failure**

CAUSES:

- Idiopathic
- Ischemia with prior MI(MOST COMMON)
- Valvular disease
- Tachycardia-induced
- Hereditary causes
- Infections e.g. viral, rickettsial, bacterial, fungal, protozoal, metazoal
- Peri-partum cardiomyopathy (occurs in last trimester or in 6 months post-partum)
- Endocrinologic causes e.g. hyperthyroidism, hypothyroidism, diabetes mellitus, myxedema, hypoparathyroidism, acromegaly
- Connective tissue disorders e.g. scleroderma, RA, SLE, dermatomyositis
- Nutritional e.g. thiamine deficiency, protein deficiency, starvation, carnitine deficiency,
- doxorubicin
- Toxins e.g. cobalt, lead, phosphorus,
- Alcoholism
- Drugs e.g. anthracycline derivatives, VEGF inhibitors, alcoholism, anti-retroviral agents
- Infiltrative e.g. hemochromatosis, amyloidosis
- Granulomatous e.g. sarcoidosis, giant cell myocarditis
- Neuromuscular disorders e.g. Duchenne dystrophy, Erb dystrophy
- Stress induced (Takotsubo cardiomyopathy)
- Smoker heavy
- Tachycardiomyopathy

PATHOPHYSIOLOGY:

- Systolic dysfunction

PRESENTATION:

- Symptoms and signs of left- and right-sided heart failure
- Presence of functional murmurs (MR, TR)
- Arrhythmias mostly atrial fibrillation, PVCs or VT

INVESTIGATIONS:

- Tests for underlying causes: CBC, Electrolytes, calcium, phosphorus, Thyroid function tests, Iron studies
- Cardiac biomarkers
- BNP
- Chest x-ray
- ECG
- Echocardiography
- Cardiac MRI

- Endomyocardial biopsy
- Cardiac catheterization: elevated right and left ventricular end diastolic pressures, reduced or normal EF and does not increase in response to exercise.

TREATMENT:
Management is same as heart failure.
- ACE inhibitors/ ARBs
- Beta-blockers
- Aldosterone antagonists
- Cardiac glycosides if refractory to treatment
- Diuretics to relieve congestion
- Nitrates and vasodilators to reduce afterload
- Ivabradine to control heart rate in patients who have heart rate >70 beats/min despite maximum dose of beta blockers or have contraindication to use of beta blockers.
- Anticoagulation in selected patients
- Anti-arrhythmics if needed
- CPAP in patients with severe refractory pulmonary edema
- For patients whose disease is refractory to medical therapy: LV assist devices, cardiac resynchronization therapy, ICDs
- Heart transplantation if all above fail.
- Treat underlying cause

⇨ ***Dilated cardiomyopathy is the most common type of cardiomyopathy.***

4.7.2. HYPERTROPHIC CARDIOMYOPATHY

"It is an inappropriate myocardial hypertrophy that results in impaired relaxation of heart and diastolic dysfunction, and may be accompanied by left ventricular outflow obstruction."

QUICK FACTS: HYPERTROPHIC CARDIOMYOPATHY	
Pathology:	**Diastolic dysfunction** **In case of HOCM → LVOT**
Presentation:	**Exercise dyspnea, angina, pre-syncope, syncope, palpitations, sudden death** **Presyncope or syncope after valsalva maneuver, double apex beat, S4**
Diagnosis:	**Ejection systolic murmur** **Echocardiography**
Treatment:	**Avoid dehydration** **Beta-blockers or calcium channel blockers** **Myomectomy**

CAUSES:
- Autosomal dominant mutations (so family history is important)
- Spontaneous mutations

PATHOPHYSIOLOGY:
- Non-compliant ventricles → diastolic dysfunction → increased LV EDP
- In case of HOCMP: outflow obstruction

AGGRAVATING FACTORS:
- Increased heart rate, increased contractility, decreased LV filling (e.g. valsalva maneuver, dehydration, diuresis)

PRESENTATION:
- Symptoms:

- Exertional dyspnea, angina, presyncope or syncope (after exercise or valsalva maneuver), palpitations, sudden death
- Signs:
  - Presyncope or syncope (after valsalva maneuver), arrhythmias, double apex beat, loud S4
  - Ejection systolic murmur:
    - Heard at left lower sternal area
    - Decreases with increase venous return and decreased outflow obstruction: squatting, lying down, straight leg-raise test.
    - Decreases with increased peripheral vascular resistance: sustained hand-grip.
    - Increases with decreased venous return and thus decreased LV size: Valsalva and standing.

INVESTIGATIONS:

- Echocardiography:
  - Shows hypertrophied ventricles, asymmetrical septal hypertrophy, systolic anterior motion of anterior mitral leaflet, LV outflow obstruction (sub-aortic stenosis).

MANAGEMENT:

- General advice: avoid strenuous exercise, dehydration, diuretics
- Screen first-degree relatives.
- Asymptomatic patients: no treatment.
- Symptomatic patients:
  - Beta-blockers
  - Calcium channel blockers especially verapamil
  - Diuretics only in fluid overload
  - Surgical treatment: myomectomy
  - Treatment of complications

4.7.3. RESTRICTIVE CARDIOMYOPATHY

"It is a condition of increased stiffness of myocardium due to infiltration or fibrosis that results in impaired relaxation and diastolic dysfunction".

QUICK FACTS: RESTRICTIVE CARDIOMYOPATHY	
Pathology:	**Diastolic dysfunction**
Presentation:	**Dyspnea, exercise intolerance**
	Right heart failure
	Arrhythmias
Diagnosis:	**Echocardiography**
Treatment:	**Treat underlying cause**
	Management of heart failure

CAUSES:

- Infiltrative disorders like amyloidosis, sarcoidosis, hemochromatosis, scleroderma, glycogen storage diseases
- Carcinoid syndrome
- Chemotherapy or radiation induced
- Idiopathic
- Endocardial fibroelastosis = diffuse cartilaginous endocardial thickening and myocardial dysfunction
- Endomyocardial fibrosis = patchy fibrosis of endocardium leading to restrictive cardiomyopathy
- Eosinophilic cardiomyopathy (Loeffler's endocarditis)

PATHOPHYSIOLOGY:

- Decreased ventricular compliance → impaired ventricular filling → reduced diastolic volumes

PRESENTATION:

- Elevated LV filling pressures: dyspnea, exercise intolerance
- Symptoms and signs of right heart failure

- Kussmaul's sign may be present.
- Arrhythmias e.g. atrial fibrillation

INVESTIGATIONS:

- Echocardiogram:
  - Thickened myocardium
  - Systolic dysfunction
  - Increased size of RA and LA
  - Normal size of RV and LV
- ECG:
  - Low voltage ECG
  - Atrial fibrillation
- Chest x-ray
  - Findings of heart failure
- Cardiac catheterization:
  - Distinguishes between restrictive cardiomyopathy and constrictive pericarditis.
  - Restrictive cardiomyopathy:
    - Left more involved than right
    - PCWP > right atrial pressure
    - PASP >50 mmHg
  - Constrictive cardiomyopathy:
    - Left and right equally involved
    - PCWP = right atrial pressure
    - PASP <50 mmHg

MANAGEMENT:

- Treatment of underlying disease e.g. hemochromatosis, sarcoidosis
- Digoxin (in case of systolic dysfunction). Avoid in amyloidosis.
- Drugs which decrease preload should be given with caution e.g. vasodilators, diuretics
- Diuretics in case of overload

4.7.4. ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

It is a condition of fibro-fatty infiltration of ventricles primarily of right side that predisposes to ventricular tachyarrhythmias and sudden death.

4.7.5. MYOCARDITIS

"It is a condition of myocardial inflammation that leads to dilated cardiomyopathy".

QUICK FACTS: MYOCARDITIS	
Pathology:	**Myocardial inflammation → cardiac dysfunction**
Presentation:	**Recent history of flu-like illness** **Fatigue, dyspnea, chest pain, muscle aches, fever** **Heart failure**
Diagnosis:	**Clinical diagnosis** **Raised cardiac markers** **Antimyosin scintigraphy** **Echocardiography, Gd-MRI, endomyocardial biopsy**
Treatment:	**Treat underlying cause** **Management of heart failure**

Table 4.20. CAUSES OF MYOCARDITIS			
Viral	Coxsackie B virus (most common cause) Adenovirus Epstein-Barr virus Influenza Cytomegalovirus Poliomyelitis HIV Hepatitis C virus	**Bites**	Scorpion venom Snake venom Black widow spider venom
Bacterial	Acute rheumatic fever Diphtheria	**Drugs**	Penicillins Methyldopa Streptomycin Doxorubicin Phenytoin Amphetamines Cocaine Catecholamines
Rickettsial	Scrub typhus Q fever Rocky mountain spotted fever	**Chemicals**	Carbon monoxide Arsenic Lead
Spirochaetal	Syphillis Lyme's disease Relapsing fever Leptospirosis	**Physical agents**	Heat stroke Radiation Hypothermia
Protozoal	Chagas disease (American trypanosomiasis) Toxoplasmosis Leishmaniasis Malaria	**Systemic**	Giant cell myocarditis Kawasaki's disease Inflammator bowel disease SLE RA Thyrotoxicosis
Fungal	Candida Aspergillus	**Peripartum cardiomyopathy**	

PRESENTATION:

- Patients present as rapidly progressive heart failure/ arrhythmias.
- Recent history of flu-like illness (in case of viral myocarditis).
- Fatigue, palpitations, dyspnea, precordial discomfort, muscle aches, fever, sweats
- Signs of heart failure
- Signs of related disorders e.g. sarcoidosis

INVESTIGATIONS:

- Diagnosis is based on history, recent history of viral illness and suspicion.
- CRP, ESR may be raised
- Cardiac markers are raised
- Antimyosin scintigraphy identifies myocardial inflammation
- Echocardiography
- Coronary angiography to rule out ischemia
- Gd-MRI
- Endomyocardial biopsy is diagnostic however only recommended in patients not responding to medical therapy.

MANAGEMENT:

- Treat underlying cause.
- Restrict physical activity.
- Treat as congestive heart failure vasodilators, diuretics, ACE inhibitors.
- Consider anticoagulation
- Inotropes like dobutamine or milrinone in severe cases.
- Treat arrhythmias carefully with beat-blockers or anti-arrhythmics.
- Ventricular assist devices or extra-corporeal membrane oxygenation (ECMO)
- Consider heart transplant

4.7.6. TAKOTSUBO CARDIOMYOPATHY

Aka apical ballooning syndrome, acute stress cardiomyopathy, broken heart syndrome

"It is defined as a transient condition of left ventricular akinesis following severe emotional, psychological or physical stress."

QUICK FACTS: TAKUTSOBO CARDIOMYOPATHY	
Pathology:	**Massive catecholamine release or multi-vessel spam → myocardial stunning**
Presentation:	**Severe stress state → chest pain, dyspnea, palpitations, syncope** **Features of shock or heart failure**
Diagnosis:	**ECG: ST elevations or depressions** **Cardiac markers: increased** **Echocardiography: dyskinesia** **Coronary angiography: to rule out IHD** **LV gram: octopus pot appearance (apical ballooning)**
Treatment:	**Treat as ACS** **Beta blockers**

PATHOGENESIS:

- Severe emotional or physical stress → unpredictable catecholamine release OR multi-vessel spasm → stunning of myocardium

SYMPTOMS:

- Chest pain after severe emotional or stress state, dyspnea, palpitations, nausea, vomiting, syncope
- Usually absence of risk factors for ischemic heart disease.

SIGNS:

- Tachycardia, hypotension, signs of shock or ventricular failure

INVESTIGATIONS:

- ECG shows ST elevations or depressions mimicking myocardial infarction.
- Cardiac markers are elevated.
- Echocardiography shows dyskinesia of LV mid-segments or apex.
- Coronary angiography is normal or shows insignificant coronary stenosis. LV gram reveals apical ballooning (*octopus pot appearance*).

MANAGEMENT:

- Maintain circulation, airway and breathing.
- Treat as acute coronary syndrome.
- Give beta-blockers when hemodynamically stable.
- Diurese in case of congestive heart failure.
- Inotropes should be used with caution.
- Intra-aortic balloon pump can improve resuscitative intervention.

Table 4.21. MODIFIED MAYO CLINIC CRITERIA FOR DIAGNOSIS OF TAKOTSUBO CARDIOMYOPATHY
1. Wall motion abnormalities of left ventricular mid-segments with or without apical involvement and extending beyond a single vascular territory. 2. Absence of obstructive coronary stenosis or acute plaque rupture 3. New ECG abnormalities or modestly elevated troponin levels 4. Absence of pheochromocytoma or myocarditis

4.8. PERICARDIAL DISEASE

4.8.1. ACUTE PERICARDITIS

"It is an acute inflammation of the pericardium."

QUICK FACTS: ACUTE PERICARDITIS	
Pathology:	**Inflammation of pericardium**
Presentation:	**Flu-like illness** **Chest pain: scratchy, relieved on sitting forward** **Pericardial friction rub**
Diagnosis:	**ECG: generalized concave upward ST elevations and PR depressions (reciprocal changes in aVR and V1)** **ESR, CRP, CPK**
Treatment:	**NSAIDs e.g. ibuprofen + colchicine** **Steroids in treatment failure**

PATHOPHYSIOLOGY:

- Normally there is 15 – 50 ml fluid in the pericardial cavity. This fluid is an ultra-filtrate of plasma. In acute pericarditis there is inflammation of pericardium which produces symptoms. There may be excessive ultrafiltration or inflammatory exudate which accumulates in the cavity.

SYMPTOMS:

- Chest pain
  - It is present in >95% and is usually sharp, sudden and pleuritic which is felt over anterior chest. It is relieved by sitting upright and leaning forward.
  - It is less likely in uremic and rheumatologic pericarditis.
- There may be history of flu-like illness, respiratory or gastrointestinal symptoms before the chest pain.

SIGNS:

- Pericardial friction rub: It is a superficial scratchy/ squeaking sound heard over the left sternal edge with diaphragm. Its intensity increases with pressure over diaphragm and the sound usually has a tri-phasic component. It also increases on leaning forward or in knee-elbow position. Intensity also increases on holding respiration which differentiates it from pleural or pleuro-pericardial rub.

Diagnosis requires two of the following:

- Typical chest pain
- Pericardial friction rub
- ECG changes
- New or worsening pericardial effusion

ECG CHANGES:

- ECG changes are due to epicardial inflammation. There are often no changes in uremic pericarditis because there is little or no inflammation of epicardium.
- ECG changes may evolve through four stages:
  - **Stage 1:** Diffuse ST elevations with reciprocal ST depressions in aVR and V1. PR elevation in aVR and PR depression in limb leads, V5 and V6.
  - **Stage 2:** Normalization of changes
  - **Stage 3:** Diffuse T inversions
  - **Stage 4:** Normalization of ECG or persistence of T inversions

OTHER TESTS:

- White blood cell count may be increased.
- ESR and CRP may be elevated.
- Echo may show effusion and rarely tamponade.
- Cardiac biomarkers may be elevated (typically CPK). Troponins and CK-MB may be raised if there is concomitant myocarditis.

- Chest x-ray is usually normal. At least 200 ml of pericardial fluid must accumulate before increased cardiothoracic ratio can be demonstrated.
- Blood cultures are sent if there is fever.
- CT scan will show non-calcified pericardial thickening with pericardial effusion. Active inflammation is indicated by contrast enhancement.

MANAGEMENT:

- For viral etiology non-steroidal anti-inflammatory drugs are the mainstay of treatment.
- IBUPROFEN 300 – 800 mg q8h (for one to two weeks) + COLCHICINE 0.6 mg BD (for three months)
- Colchicine reduces rates of recurrent pericarditis.
- Steroids (PREDNISONE 0.25 – 1 mg/ kg) are used along with colchicine in case of treatment failure, connective tissue diseases and uremia.
- Third generation cephalosporins plus vancomycin is used in bacterial etiology.
- Four drug ATT with a tapering dose of steroids are given for pericardial tuberculosis.
- Immediate hemodialysis without heparin in case of uremic pericarditis.

4.8.2. CONSTRICTIVE PERICARDIITS

"It is the fibrous scarring and thickening of pericardium which leads to obliteration of pericardial cavity and restriction of diastolic filling of ventricle."

QUICK FACTS: CONSTRICTIVE PERICARDITIS	
Pathology:	**Chronic inflammation of pericardium → fibrous scarring → reduced diastolic filling**
Presentation:	**Lower limb swelling, abdominal distension, dYspnea on exertion, fatigue, exercise intolerance** **Edema, ascites, pleural effusion, jugular venous distension, prominent x and y descents, Kussmaul's sign, pericardial knock**
Diagnosis:	**ECG: low voltage, T wave flattening or inversion** **Echocardiography** **CT/ MRI** **Cardiac catherization: equalization of pressures in all four chambers, square-root sign**
Treatment:	**Treat underlying cause** **Pericardiocentesis** **Pericardiectomy**

PATHOPHYSIOLOGY:

- Chronic inflammation leads to fibrous scarring of the pericardium which leads to reduced diastolic filling of heart. Impaired ventricular filling leads to decreased cardiac output. Congestive heart failure especially right-sided heart failure develops which leads to edema and ascites.

CAUSES:

- Idiopathic (most common), post-viral pericarditis, post-bacterial pericarditis, uremia, radiotherapy, tuberculosis, chronic pericardial effusion, tumor invasion, connective tissue disorders, previous pericardial surgery, drugs (procainamide, hydralazine)

SYMPTOMS:

- Due to overload: dependent lower limb swelling, abdominal distension, shortness of breath
- Due to reduced cardiac output: dyspnea on exertion, fatigue, exercise intolerance, severe weight loss

SIGNS:

- Ill-look, dependent edema, ascites, pleural effusion, raised jugular venous pressures, prominent "x" and "y" descents, Kussmaul's sign (loss of inspiratory decline in JVP), pericardial knock (an early diastolic third heart sound that occurs due to sudden cessation of ventricular filling), cachexia.

INVESTIGATIONS:

- Hyponatremia (dilutional), metabolic acidosis, congestive transaminitis, hypoalbuminemia
- ECG: low voltage QRS, generalized T wave flattening or inversion, atrial fibrillation.
- Echocardiogram: increased pericardial thickness, sharp halt in ventricular filling, atrial enlargement.
- CT/MRI: pericardial thickening and calcification.
- Cardiac catheterization: equalization of pressures in all heart chambers, rapid and steep 'x' and 'y' descent, "square root sign OR dip-and-plateau waveform" (steep 'y' descent on right and left atrial pressure waveform tracings which increases abruptly and then is sustained until systole).

TREATMENT:

- Diuretics, steroids in sub-acute constrictive pericarditis, treatment of underlying cause (e.g. ATT in tuberculosis), treatment of atrial arrhythmias. Avoid beta-blockers and calcium channel blockers. Pericardiectomy is definitive treatment.

4.8.3. PERICARDIAL EFFUSION

"Pericardial effusion is the presence of an abnormal amount or character of pericardial fluid in pericardial space."

QUICK FACTS: PERICARDIAL EFFUSION	
Pathology:	**Increased fluid in pericardial cavity → reduced diastolic filling**
Presentation:	**Asymptomatic** **Chest discomfort, light-headedness, dizziness, syncope** **Soft apex beat, muffled heart sounds**
Diagnosis:	**Chest x-ray: enlarged cardiac silhouette, water-bottle appearance** **ECG: low voltage QRS, electrical alternans** **CT/ MRI** **Pericardial fluid analysis**
Treatment:	**Pericardiocentesis, diuresis** **Treat underlying cause**

SYMPTOMS:

- Asymptomatic, chest pain or discomfort, light-headedness, dizziness, syncope, palpitations, cough, hiccups.

SIGNS:

- Soft apex beat, muffled heart sounds, dullness at left lung base, pericardial friction rub.

INVESTIGATIONS:

- Echocardiogram: (imaging of choice) can show as little as 20 ml of fluid.
- Chest x-ray: enlarged cardiac silhouette (>250 ml fluid), water-bottle appearance, enlarged heart without pulmonary vascular congestion.
- ECG: low voltage QRS, T wave flattening, electrical alternans.
- CT/MRI
- Pericardial fluid analysis: may indicate etiology of effusion
- If in doubt about etiology of pericardial effusion, then check for tuberculosis, nephrotic syndrome, renal failure, myxedema, SLE and connective tissue disorders and primary tumors e.g. lung, breast.

TREATMENT:

- Pericardiocentesis (if hemodynamically unstable or signs of cardiac tamponade in echo)
- Diurese
- Treatment of underlying cause.
- Follow-up echocardiogram in one to two weeks if effusion is small.

4.8.4. PERICARDIAL TAMPONADE

"Pericardial tamponade is the accumulation of fluid in pericardial cavity at a sufficient rate which impairs diastolic filling of heart to such an extent that cardiac output fails to maintain adequate circulation."

QUICK FACTS: PERICARDIAL TAMPONADE	
Pathology:	**Increased fluid in pericardial cavity → reduced diastolic filling → decreased**
Presentation:	**Dyspnea, weakness, confusion** **Tachycardia, hypotension, pulsus paradoxus** **Jugular venous distension, distant heart sounds, peripheral edema, hepatomegaly**
Diagnosis:	**Echocardiogram: diastolic collapse of RA and RV** **Cardiac catheterization: Equalization of diastolic pressures in all chambers, preserved x descent with absent y descent**
Treatment:	**Iv fluids** **Pericardiocentesis (immediate)**

PATHOPHYSIOLOGY:

- Pericardial effusion accumulates around heart at such a rate that pericardial compliance fails. This results in impaired ventricular filling during diastole and equalization of diastolic pressures in all chambers of heart. This in turn leads to decreased cardiac output.

ETIOLOGY:

- Any cause of pericardial effusion can lead to tamponade. Most commonly from pericarditis (metastatic, uremic, viral)

SYMPTOMS:

- Usually sudden onset of dyspnea, weakness and confusion

SIGNS:

- Signs of hemodynamic compromise: tachycardia, hypotension, pulsus paradoxus
- Others: Jugular venous distension with preserved x descent but loss of y descent, distant heart sounds
- Beck's triad = Jugular venous distension + distant heart sounds + hypotension
- In subacute tamponade: peripheral edema, hepatomegaly, ascites

INVESTIGATIONS:

- ECG: Low-voltage ECG (especially limb leads), electrical alternans
- CXR: Increased cardiothoracic ratio with obtuse cardiophrenic angles (seen if effusion volume >250 ml)
- Echocardiogram: RA and RV collapse during diastole; swinging motion of heart; abnormal inspiratory increase in tricuspid valve flow and abnormal inspiratory decrease in mitral valve flow,
- Cardiac catheterization: equalization of diastolic pressures in all chambers; preserved x descent of right atrial pressure with absent y descent.

TREATMENT:

- Immediate pericardiocentesis to prevent hemodynamic collapse.
- Fluid resuscitation to increase diastolic filling pressures. Positive inotropes (dopamine, dobutamine) may be added if hypotension severe.
- Avoid diuretics or vasodilators.

4.9. BRADYARRHYTHMIAS

Bradyarrhythmias have two main mechanism of generation:

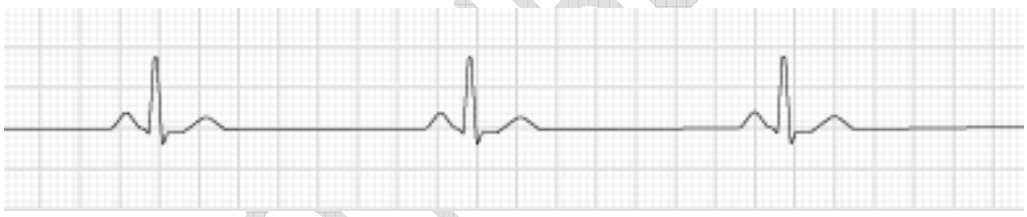
- Failure of impulse initiation
- Impaired electrical conduction

4.9.1. SINUS BRADYCARDIA

"Sinus bradycardia is a slowed sinus rhythm with heart rate less than or equal to 60 beats per minute."

- Symptomatic bradycardia usually occurs at a rate less than 50 beats per minute.

Table 4.22. CAUSES OF SINUS BRADYCARDIA
Physiological causes • Sleep • Athletic training • Young adults
Pathological/ iatrogenic causes: • Drugs like beta-blockers, centrally acting calcium channel blockers, digoxin, amiodarone, class I anti-arrhythmic agents. Lithium, paclitaxel, fentanyl, reserpine, clonidine. • Inferior wall myocardial infarction • Sick sinus syndrome • Hypothyroidism • Hypothermia • Hypoglycemia • Sleep apnea



SYMPTOMS:

- Asymptomatic, syncope, dizziness, light-headedness, chest pain, shortness of breath, exercise intolerance

SIGNS:

- Asymptomatic, decreased level of consciousness, cyanosis, edema, heart failure, dyspnea, syncope, poor tissue perfusion

INVESTIGATIONS:

- ECG

MANAGEMENT:

- If asymptomatic, no treatment needed.
- Look for causes of bradycardia and treat them.
- If symptomatic: may give injection atropine 0.5 mg IV SOS every 3 – 5 minutes till a total dose of 3 mg OR start on DOPAMINE infusion @ 2- 10 µg/kg/min OR ADRENALINE infusion @ 2 – 10 µg/min

4.9.2. SINUS NODE DISEASE

- SA node dysfunction may be intrinsic or extrinsic. Extrinsic causes are usually reversible.

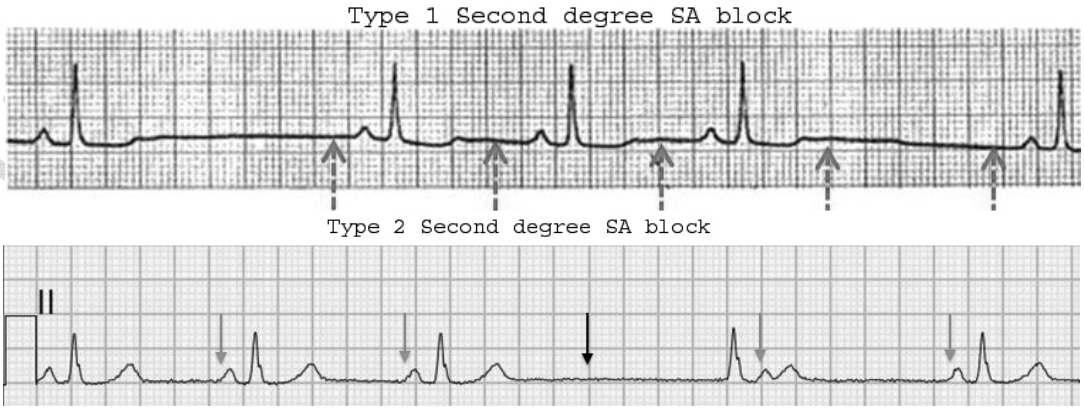
Table 4.23. CAUSES OF SA NODE DISEASE	
EXTRINSIC	**INTRINSIC**
Carotid sinus hypersensitivity Vasovagal syncope Drugs e.g. beta-blockers, calcium channel blockers, digoxin, anti-arrhythmics (class I and III), adenosine, ivabradine Electrolyte abnormalities e.g. hyperkalemia Hypothyroidism Sleep apnea syndrome Vagal maneuvers Hypothermia Raised intra-cranial pressure	Sick sinus syndrome (idiopathic degenerative fibrosis) Coronary artery disease Inflammatory conditions e.g. pericarditis, rheumatic heart disease, Lyme disease Senile amyloidosis Iatrogenic Radiation therapy Chest trauma Congenital conditions e.g. Kearns-Sayre syndrome, myotonic dystrophy

PRESENTATION:

- Asymptomatic, dizziness, light-headedness, chest pain, shortness of breath, exercise intolerance, hypotension, presyncope, syncope

ECG:

- Sinus bradycardia = sinus rate <60 beats/min
- Sinus arrhythmia = variable sinus cycle lengths (exclude respiratory association)
- Sinus pauses = transient absence of sinus P wave seconds (cycle length is not a multiple of basic sinus cycle length)
- Sinus arrest = a sinus pause >3 seconds
- Sinus exit block =
    - First degree SA block: delay between impulse generation and transmission to atria (undetectable on ECG).
    - Second degree SA block type 1: progressive shortening of P-P interval till a dropped P wave.
    - Second degree SA block type 2: intermittent dropped P waves while subsequent P wave appears on time.
    - Third degree SA block: complete absence of P waves.
- Tachycardia-bradycardia syndrome = alternating bradycardia and escape tachycardias. Tachycardias include atrial tachycardia, atrial flutter and atrial fibrillation (most common).
- Chronotropic incompetence = failure to increase heart rate with exercise.



INVESTIGATIONS:

- ECG

- Holter monitor
- Event monitor
- Electrophysiologic testing

MANAGEMENT:

- Correct extrinsic causes.
- Pacemaker insertion.
- Oral theophylline (off the label treatment).

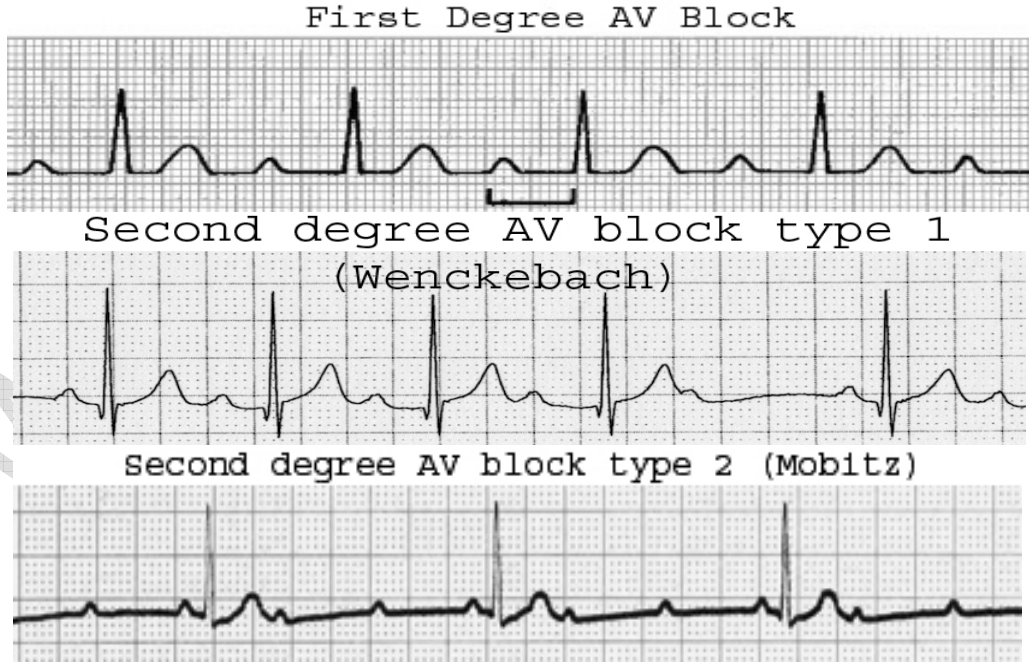
⇨ ***SA node is supplied by right coronary artery in 60% and left circumflex artery in 40%.***

⇨ ***Commonest cause of sinus node dysfunction is idiopathic degenerative fibrosis.***

⇨ ***Commonest risk factor of sinus node dysfunction is ageing.***

4.9.3. ATRIOVENTRICULAR NODE DISEASE

- Impulse generating from SA node reaches AV node via inter-nodal pathways where it experiences a conduction delay. This delay is represented on ECG by PR interval (Interval from start of P till the beginning of QRS complex = 0.12 – 0.2 seconds). This inter-nodal conduction may be impaired by a variety of causes. Depending on the severity of disease there may be a prolonged delay in conduction or blockage of conduction of some impulses.
- **First degree AV block:**Wide fixed PR interval >0.20 seconds
- **Second degree AV block:** Intermittent drop of ventricular beat. It is of two types:
  - **Type I (aka Mobitz type 1 or Wenkebach type):** Block is in proximal system. There is progressive increase in PR interval until a ventricular beat is dropped. QRS is narrow.
  - **Type II (aka Mobitz type 2 or Mobitz type):** Block is in distal or infra-His conduction system. There is intermittent failure in conduction of P waves without change in preceding PR or RR intervals.
- **Third degree AV block (aka complete heart block):** complete failure of conduction from atria to ventricles. There is P to QRS dissociation.



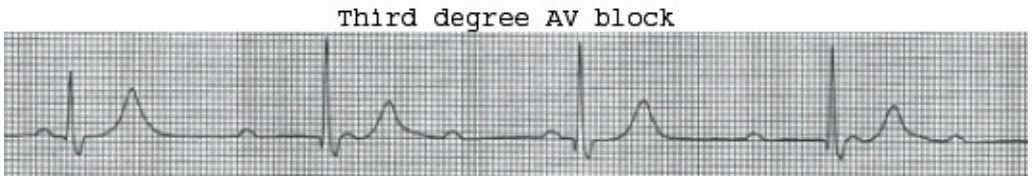


Table 4.24. CAUSES OF AV NODE DISEASE			
Autonomic	Carotid sinus hypersensitivity Vasovagal syncope	**Congenital**	Maternal SLE Kearns-Sayre syndrome Myotonic dystrophy
Metabolic/ endocrine	Hyperkalemia Hypermagnesemia Hypothyroidism Adrenal insufficiency	**Inflammatory**	SLE Mixed connective tissue disease Rheumatoid arthritis Scleroderma
Drugs	Beta-blockers Calcium channel blockers Adenosine Digitalis Lithium Antiarrhythmics (class I and III)	**Neoplastic**	Lymphoma Mesothelioma Melanoma
Infectious	Endocarditis Lyme disease Chagas disease Tuberculosis Diphtheria Syphilis toxoplasmosis	**Infiltrative**	Amyloidosis Sarcoidosis Hemochromatosis
Degenerative	Lev disease	**Others**	Coronary artery disease Radiation

PRESENTATION:

- Asymptomatic, dizziness, light-headedness, chest pain, shortness of breath, exercise intolerance, hypotension, presyncope, syncope

MANAGEMENT:

- First degree AV block: no treatment necessary.
- Asymptomatic second degree AV block:
  - No treatment necessary.
  - Treat any correctable factors.
- Symptomatic second degree or any third degree AV block:
  - Atropine, dopamine or adrenaline infusion
  - Transcutaneous or transvenous pacing.
  - Treat reversible causes.
  - If no reversible cause then permanent pacing.

4.9.4. VASOVAGAL SYNCOPE

Aka reflex syncope

"It is a transient self-limited loss of consciousness due to malfunction of sympathetic nervous system upon certain triggers e.g. sight of blood or intense emotional stimuli."

PATHOPHYSIOLOGY:

- Triggers → activate nuclei in brain-stem → simultaneous activation of parasympathetic nervous system and withdrawal of sympathetic nervous system → decreased heart rate and blood pressure → decreased blood flow to brain

INVESTIGATIONS:

- Tilt-table test, ECG, echocardiography, Holter monitoring, electrophysiology

MANAGEMENT:

- Avoid triggers. Give CNS stimulants

4.10. TACHYARRHYTHMIAS AND PULSELESS ELECTRICAL ACTIVITY/ ASYSTOLE

Tachyarrhythmias may be generated by following mechanisms:

- Paced impulse generation in response to a physiological stimulus
- Paced impulse generation due to irritable foci
- Re-enterant pathways

Table 4.25. CLASSIFICATION OF TACHYARRHYTHMIAS

	Narrow	Wide
Regular	**Short RP** Slow-Fast AVNRT Slow-slow AVNRT Orthodromic AVRT Junctional tachycardia Atrial tachycardia	Any of following with aberrancy: Sinus tachycardia, atrial tachycardia, junctional tachycardia, AVNRT, orthodromic AVRT, atrial flutter Antidromic AVRT Monomorphic VT
	Long RP Fast-slow AVNRT Orthodromic AVRT (slow accessory pathway) Sinus tachycardia Atrial tachycardia Paroxysmal junctional reciprocating tachycardia	
	Flutter waves Atrial flutter with fixed block	
Irregular	Atrial fibrillation Atrial flutter with variable block Multi-focal atrial tachycardia	Any of following with rate-related or fixed aberrancy: atrial fibrillation, atrial flutter with variable block, multi-focal atrial tachycardia Polymorphic VT/ Torsades des pointes Ventricular fibrillation

Table 4.26. APPROACH TO NARROW COMPLEX TACHYARRHYTHMIAS

Regular	P waves visible	Atrial rate > ventricular rate			Atrial flutter Atrial tachycardia
		Atrial rate not greater than ventricular rate	RP < PR	RP <70 ms	AVNRT
				RP >70 ms	AVRT AVNRT Atrial tachycardia
			RP > PR		Atrial tachycardia Junctional tachycardia Atypical AVNRT
	P waves not visible				AVNRT
Irregular					Atrial fibrillation Atrial tachycardia with variable block Atrial flutter with variable block Multifocal atrial tachycardia

4.10.1. SINUS TACHYCARDIA (ST)

"Sinus tachycardia is a fast sinus rhythm with heart rate greater than or equal to 100 beats per minute."

- Usually the rate of sinus tachycardia is ≤150 beats per minute in elderly (can be up to 200 per minute in young).
- **Appropriate sinus tachycardia:** physiological response to maintain cardiac output.
- **Inappropriate sinus tachycardia:** sinus tachycardia without secondary causes

Table 4.27. CAUSES OF SINUS TACHYCARDIA

Physiological causes
Anxiety
Exercise
Pathological/ iatrogenic causes:
Fever
Anemia
Hypovolemia
Drugs like beta-agonists, atropine, catecholamines, methylxanthines, nitrates, amphetamines
Congestive heart failure
Pulmonary disease e.g. asthma exacerbation, COPD exacerbation, pulmonary embolism
Thyrotoxicosis
Caffeine, nicotine
Withdrawal from drugs

SYMPTOMS:

- Asymptomatic, palpitations, feeling anxious

SIGNS:

- Tachycardia, heart failure, worsening of heart failure and ischemia

TREATMENT:

- Treat the cause.
- In case of inappropriate sinus tachycardia: beta-blockers, rate-limiting calcium channel blockers

4.10.2. FOCAL ATRIAL TACHYCARDIA (FAT)

"It is a fast atrial rhythm with atrial rate greater than 100 beats per minute."

RISK FACTORS:

- Structural heart disease, drugs (e.g. beta-agonists, amphetamine, methyl-xanthines), digitalis toxicity

PRESENTATION:

- Palpitations (sudden episodic), dyspnea, dizziness, light-headedness, chest heaviness

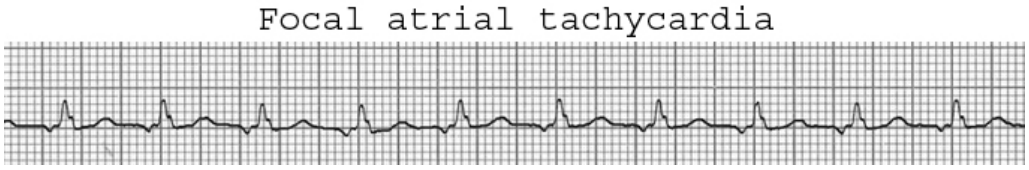
ECG:

- Abnormal P wave not meeting criteria for sinus rhythm in lead II, rate >100/min

MANAGEMENT:

- Manage precipitating conditions.
- May need electrophysiology.
- Carotid massage and adenosine do not suppress atrial tachycardias.
- Rate control agents: beta-blockers, non-dihydropyridine calcium channel blockers.
- Class IA and III anti-arrhythmics may be considered.
- Cardioversion can be considered in hemodynamically unstable patients.

- Radiofrequency catheter ablation.



⇨ ***Most common tachycardia associated with digoxin toxicity is atrial tachycardia with 2:1 block.***

4.10.3. MULTI-FOCAL ATRIAL TACHYCARDIA (MAT)

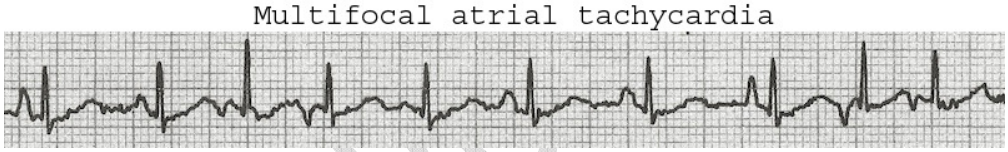
"It is a fast rhythm originating from multiple atrial foci."

RISK FACTORS:

- Severe pulmonary disease e.g. COPD, coronary artery disease, valvular heart disease, post-surgery, diabetes, hypokalemia

ECG:

- P waves of at least three different morphologies
- Atrial rate greater than 100 beats per minute
- Irregularly irregular rhythm
- Variable PR intervals



TREATMENT:

- Manage underlying cause.
- Improve hypoxia. Correct electrolytes and magnesium.
- In patients with preserved LV function: oral calcium channel blockers, beta-blockers, digoxin, amiodarone or IV flecainide or IV propafenone.
- High dose IV magnesium sulfate can be used.
- In patients with compromised LV function: use digoxin, diltiazem or amiodarone.
- Electrical cardioversion is contraindicated as it is ineffective.

⇨ ***Wandering pacemaker rhythm is a slowed MAT i.e. atrial rate less than 100 beats/min.***

4.10.4. SINUS NODE RE-ENTERANT TACHYCARDIA (SNRT)

"It is a tachycardia with re-enterant pathway opening near sinus node."

- It is almost impossible to differentiate it from sinus tachycardia on ECG.
- It is acutely managed with vagal maneuvers or adenosine.
- Chronic suppression is done with verapamil, digoxin or catheter ablation.

4.10.5. ATRIAL FIBRILLATION (AF)

"Atrial fibrillation is an abnormal chaotic irregular rhythm due to re-enterant pathway which impedes a functional co-ordinated atrial contraction."

QUICK FACTS: ATRIAL FIBRILLATION	
Pathology:	**Re-enterant circuit → atrial fibrillation → deprives of atrial kick (important in heart failure), thrombo-embolism and in the long-run tachycardiomyopathy**
Presentation:	**Palpitations, dyspnea, chest pain, pre-syncope, syncope Embolic phenomenon, worsening of heart failure or angina, hypotension Tachycardia-induced cardiomyopathy**
Diagnosis:	**Pulse examination ECG: irregularly irregular rhythm, wavy baseline, absence of definite P wave Holter or event monitoring, exercise testing**
Treatment:	**Acute AF with life-threatening instability: electrical cardioversion with peri-procedure heparin Acute AF without life threatening instability: chemical cardioversion with peri-procedure heparin >48 hours duration with hemodynamic instability: immediate cardioversion with peri-procedure heparin and continue anticoagulation >48 hours without hemodynamic instability: If there is need for early cardioversion: rule out LA thrombus with TEE and cardiovert with peri-procedure heparin. Continue anticoagulation for 4 weeks. If there is clot then do anticoagulation for 3 weeks before cardioversion. If there is no need for early cardioversion: anticoagulation for 3 weeks then attempt cardioversion and keep on anticoagulation for 4 weeks. Paroxysmal or persistent AF: choose rate vs rhythm control strategy + anticoagulation + ACEI or ARB**

- Patients with this disorder experience increased strokes, left ventricular dysfunction, depression and death.

ECG FEATURES OF ATRIAL FIBRILLATION:

- Irregularly irregular R-R intervals
- Absence of distinct P waves
- Absence of iso-electric line
- Presence of fine (amplitude <0.5mm) or coarse (amplitude >0.5 mm) fibrillatory waves.
- Frequency of fibrillatory waves around 300-600/ min.
- For classification purposes, atrial fibrillation episodes should last more than 30 seconds.

PATHOGENESIS:

- Re-enterant current initiation occurs by one of the two mechanisms:
  - Haissaguerre model: focal initiation in pulmonary veins by a trigger and local re-entry
  - Moe-Abildskov model: multiple wavelets cut by rotors
- Atrial fibrillation deprives the ventricles of atrial kick which under normal conditions contributes 25% of ventricular end-diastolic volume. In case of heart failure, loss of this kick deprives the heart of a significant amount of blood.
- Stasis of blood due to helter-skelter contractions and activation of platelet-activating factor leads to a hypercoagulable state inside heart.

TYPES OF ATRIAL FIBRILLATION:

- **Paroxysmal/ intermittent:** atrial fibrillation that comes in episodes lasting less than seven days and terminates spontaneously or has to be terminated.
- **Persistent:** continuous atrial fibrillation that lasts more than seven days and has to be terminated or gets terminated spontaneously.

- **Long-standing persistent:** persistent atrial fibrillation that lasts for more one year.
- **Permanent:** continuous atrial fibrillation in which it has been decided by the patient or doctor not to restore sinus rhythm.
- **Recurrent:**>2 episodes of atrial fibrillation
- **First-onset or first-detected:** atrial fibrillation which has not been diagnosed before.
- **Lone:** there is absence of cardiac or pulmonary disease as well as hypertension, diabetes, hyperthyroidism, acute infections, recent cardiothoracic or abdominal surgery, and systemic inflammatory diseases. It is usually seen I younger people.
- **Post-operative:** new onset atrial fibrillation (usually self-terminating) after major (typically cardiac) surgery in patients with no history of AF.
- **Valvular:** atrial fibrillation in patients with mitral stenosis or artificial valves (or valve repair according to some). Atrial fibrillation in conditions like mitral regurgitation, aortic stenosis or aortic regurgitation do not result in low flow in atrium and therefore is not classified as being valvular.
- **Non-valvular:** atrial fibrillation in patients other than valvular atrial fibrillation.
- **Atrial fibrillation with slow ventricular response:** ventricular rate <60/min. It is commonly seen in case of:
    - Rate controlled atrial fibrillation
    - Atrial fibrillation with conduction delays
    - Atrial fibrillation associated with digoxin toxicity (rare)
- **Atrial fibrillation with fast ventricular response:** ventricular rate >100/min

Table 4.28. RISK FACTORS FOR ATRIAL FIBRILLATION	
Cardiac risk factors	**Non-cardiac risk factors**
Coronary artery disease Hypertension Heart failure/ cardiomyopathies Valvular heart diseases Pre-excitation syndromes Pericardial disease	Old age Obesity Diabetes mellitus Hyperthyroidism Subclinical hyperthyroidism Hypothyroidism Chronic kidney disease Chronic obstructive pulmonary disease Obstructive sleep apnea syndrome European ancestory Alcoholism Drugs e.g. sympathomimetics, ivabradine Electrolyte disturbances e.g. hypokalemia, hypomagnesemia Pulmonary embolism Acid-base disturbances Phaeochromocytoma Smoking

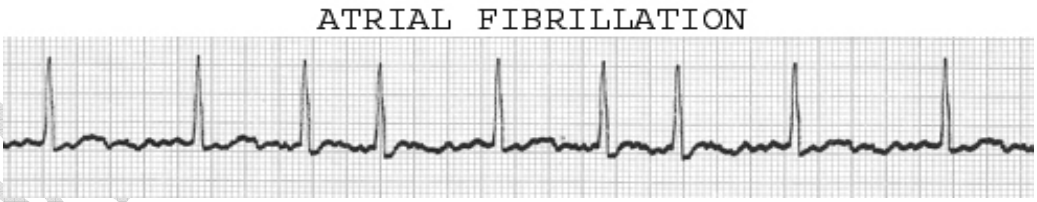


Table 4.29. MODIFIED EUROPEAN HEART RHYTHM ASSOCIATION (EHRA) CLASSIFICATION OF AF-RELATED SYMPTOMS	
EHRA I	No symptoms at all.
EHRA IIa	Mild symptoms which do not affect daily activities.
EHRA IIb	Moderate symptoms which do not affect daily activities but disturb the patient.
EHRA III	Severe symptoms which affect daily activities.
EHRA IV	Disabling symptoms which lead to discontinuation of activity.

PRESENTATION:

- Asymptomatic – usually detected on pulse examination or routine ECG
- Isolated complaints: palpitations, dyspnea, fatigue, dizziness, chest pain, pre-syncope, syncope.

- Complications: embolic complications (like stroke, gangrene, renal failure, etc.), hemodynamic complications (worsening of heart failure or angina, hypotension)
- Tachycardia-induced cardiomyopathy

INVESTIGATIONS:

- Pulse examination (screen in all patients above 65 years or having chronic risk factors)
- 12-lead ECG
- Echocardiogram (trans-thoracic or trans-esophageal)
- Exercise testing
- Holter monitoring or event recording

MANAGEMENT:

- Document ECG using a 12-lead ECG.
- Perform trans-thoracic echocardiography in all patients.
- For managementof first-detected atrial fibrillation:
    - If duration <48 hours, can be immediately cardioverted with peri-procedure heparin. If CHA_2DS_2VASc score >1 then give long-term anticoagulants (warfarin, novel anticoagulants). Electrical cardioversion is chosen in case of hemodynamic instability whereas pharmacological cardioversion is chosen if hemodynamics are stable.
    - If duration >48 hours or unknown, check for presence of hemodynamic instability (presence of active ischemia, organ hypoperfusion, severe heart failure including pulmonary edema and presence of pre-excitation syndrome need urgent cardioversion).
    - If there is presence of hemodynamic instability, then perform immediate electrical cardioversion with peri-procedure heparin. Keep patient on anti-coagulation for a minimum period of 4 weeks. Continue afterwards if there is irreversible cause and high risk of stroke (as assessed with CHA_2DS_2VASc score).Pharmacological cardioversion can be done with class IC or class III anti-arrhythmics but is less effective. Anti-arrhythmics when combined with electrical cardioversion have better results. Class IC drugs are contraindicated in structural heart disease and ischemia.
    - If no hemodynamic instability then assess whether there is need for early cardioversion or not.
    - If there is need for early cardioversion, perform a trans-esophageal echocardiogram and rule out left atrial clots. If there is no clot, cardioversion can be performed immediately and anti-coagulation continued for 4 weeks. If there is clot, then keep on anti-coagulation for 3 weeks. If thrombus resolves then attempt cardioversion and then keep on anti-coagulation for at least 4 weeks. If thrombus does not resolve then adopt rate control strategy with long-term anticoagulation.
- For management of patients with paroxysmal, recurrent or persistent atrial fibrillation:
    - Choos a strategy: rhythm versus rate control.
    - Rhythm control strategy is suitable in patients with hemodynamic instability, presence of symptoms, young age, first-onset, correctable cause and with congestive heart failure.
    - Rate control strategy is suitable for patients with age >65 years, coronary artery disease and with contraindications to cardioversion.
    - If rate control strategy is adopted then use beta-blockers ornon-dihydropyridine calcium channel blockers.
    - ACEIs or ARBs
- Ablation can be done with radiofrequency ablation or cryoballoon.
- Surgical management (in case of refractory atrial fibrillation):
    - Maze surgery

⇨ ***Atrial fibrillation is the most common chronic arrhythmia.***

4.10.6. ATRIAL FLUTTER (AFl)

"It is a re-enterant rhythm in right atrium characterized by high atrial rates and some degree of AV node conduction block."

CAUSES:

- Ischemic heart disease
- Thyrotoxicosis
- Pulmonary embolism
- Mitral valve disease
- Cardiac surgery
- COPD

PRESENTATION:

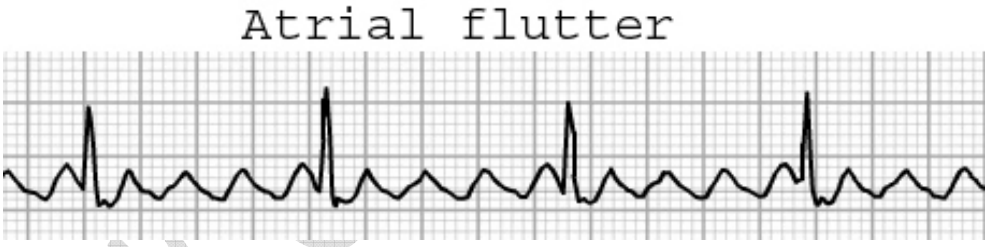
- Palpitations, fatigue, dyspnea, angina, presyncope, syncope

ECG:

- Flutter or F waves (saw-tooth shaped waves) with rate 250 – 400 beats per minute best seen in II, III, aVF.
- AV block is present e.g. 4:1. 3:1, 2:1, etc.
- Regular rhythm (in case of fixed block).
- Irregular rhythm (in case of variable block)

MANAGEMENT:

- Vagal maneuvers or adenosine may slow ventricular response and make flutter waves more prominent.
- It is the same as atrial fibrillation.



4.10.7. ATRIOVENTRICULAR NODAL RE-ENTERANT TACHYCARDIA (AVNRT)

"It is a re-enterant tachycardia with re-enterant pathways within or around the AV node."

QUICK FACTS: ATRIOVENTRICULAR NODAL RE-ENTERANT TACHYCARDIA	
Pathology:	**Two pathways within AV node → re-enterant circuit**
Presentation:	**Palpitations, chest pain, dyspnea, syncope** **Narrow complex regular tachycardia**
Diagnosis:	**ECG**
Treatment:	**Vagal maneuvers** **Iv adenosine** **Iv verapamil/ diltiazem/ esmolol/ metoprolol/ amiodarone** **DC cardioversion (if hemodynamic instability)** **Prevention: oral digoxin, beta-blockers, non-dihydropyridine calcium channel blockers**

PATHOPHYSIOLOGY:

- AV node develops two pathways, one fast pathway and one slow pathway → current undergoes re-entry through both pathways →fast tachycardia ensues

TYPES OF AVNRT:

- Typical (slow-fast):
  - Most common variety.
  - Current goes anterograde through slow pathway and retrograde through fast pathway.
  - ECG shows:
    - Narrow complex tachycardia (unless aberrancy is present)
    - Heart rate 140 – 280 beats/min
    - Absence of P waves (or hidden in QRS)
    - P waves may occur as pseudo r waves in V1-2, pseudo s waves in II, III and aVF or as pseudo q waves in inferior leads.
    - RP interval typically <70 ms.
- Atypical (fast-slow):
  - Current goes anterograde through fast pathway and retrograde through slow pathway.
  - ECG shows:
    - Narrow complex tachycardia (unless aberrancy is present)
    - Heart rate 140 – 280 beats/min
    - Inverted P waves are present between QRS and T waves (QRS-P-T complex).
- Atypical (slow-slow):
  - Current goes anterograde through slow pathway and retrograde through slow atrial fibers.
  - ECG shows:
    - P waves before QRS.
    - May be confused with sinus tachycardia.

PRESENTATION:

- Palpitations, chest pain, dyspnea, syncope, cardiac arrest

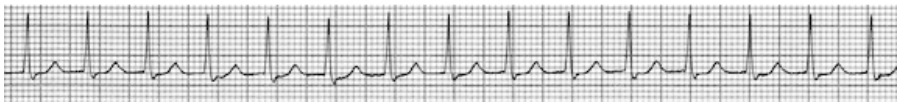
INVESTIGATIONS:

- Rule out myocardial infarction, electrolyte disturbances and hyperthyroidism.

MANAGEMENT:

- Management resolves around measures to delay AV conduction. These include:
- Acute management:
  - Vagal maneuvers
    - Valsalva maneuver in supine position (most effective)
    - Carotid massage
    - Application of ice pack to face
  - IV adenosine
    - It is given as 6 mg rapid IV bolus and is the first-line drug.
    - It can be repeated as two doses of 12 mg each.
    - It is contraindicated in case of AV blocks, COPD or asthma.
    - In case of a central line the doses are halved.
  - IV verapamil or diltiazem
    - VERAPAMIL 2.5 – 5 mg IV every 5 minutes up to a máximum of 15 mg.
    - DILTIAZEM 0.25 mg/kg IV bolus over 2 minutes. May be repeated as a 0.35 mg/kg bolus after 15 minutes or continued as a 5 g/hour infusion.
  - IV esmolol or metoprolol
    - METOPROLOL 2.5 – 5mg IV every 2 minutes up to 15 mg.
    - ESMOLOL 500 mg/kg IV bolus then 50 mg/kg/min infusion.
  - Other drugs: IV amiodarone, procainamide, propafenone, flecainide and ibutilide.
  - DC cardioversion if hemodynamic instability or refractory to medical therapy.

AVNRT



- Preventive therapy:
  - Oral digoxin, beta-blockers or non-dihydropyridine calcium cannel blockers.
  - Radiofrequency catheter ablation of AV node in case of recurrent attacks.

⇨ ***AVNRT is the most common type of supraventricular tachycardia.***

4.10.8. ATRIOVENTRICULAR RE-ENTERANT TACHYCARDIA (AVRT)

"It is a re-enterant tachycardia with re-enterant pathways involving AV node and an accessory pathway."

PATHOPHYSIOLOGY:

- Current undergoes re-entry through AV node and accessory pathway → tachycardia

PRESENTATION:

- Palpitations, chest pain, dyspnea, syncope, cardiac arrest

TYPES:

- General features include:
  - Heart rate 200 – 300 beats/min
  - ST depressions or T inversions may be present
  - Baseline ECG may reveal delta wave
- Orthodromic AVNRT: current goes anterograde through AV node and retrograde through accessory pathway.
  - Narrow complex tachycardia (unless aberrancy is present)
- Antidromic AVNRT: current goes anterograde through accessory pathway and retrograde through AV node.
  - Wide complex tachycardia (unless aberrancy is present)

MANAGEMENT:

- Same as AVNRT
- Verapamil or digoxin should be avoided.

4.10.9. VENTRICULAR TACHYCARDIA (VT)

"It is a fast rhythm originating from the ventricles."

QUICK FACTS: VENTRICULAR TACHYCARDIA	
Pathology:	**Irritable focus or re-enterant pathway within ventricle**
Presentation:	**Palpitaitons, chest pain, dyspnea, syncope, cardiac arrest** **Wide-complex tachycardia**
Diagnosis:	**ECG** **EP studies**
Treatment:	**Pulseless VT: cardiopulmonary resuscitation, defibrillation, amiodarone, lidocaine** **VT with pulse but danger signs: DC cardioversion, amiodarone** **VT with pulse and without danger signs: amiodarone, DC cardioversion** **Torsades des pointes: MgSO4** **Treat underlying cause** **Prevention: beta-blockers, amiodarone, anti-arrhythmics, ICD device**

TYPES OF VT:

- Monomorphic VT: QRS complexes are of same shape and amplitude
- Polymorphic VT: QRS complexes are of different shape and amplitude
    - Polymorphic VT with normal QT
    - Polymorphic VT with prolonged QT (Torsades de pointes)

PRESENTATION:

- Palpitations, chest pain, dyspnea, syncope, cardiac arrest

ECG:

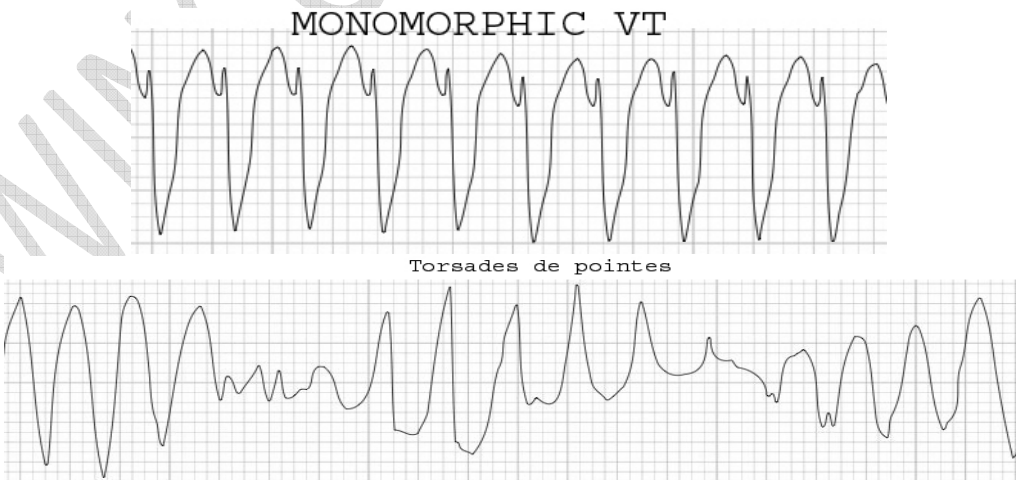
- It may be difficult to differentiate between ventricular tachycardias and supraventricular tachycardias with aberrant conduction. Points which favor VT include:
- Clinical hints: age >35 years, presence of ischemic or structural heart disease, family history of sudden cardiac death.
- ECG hints: started with a PVC, presence of AV dissociation, very broad complexes, absence of typical RBBB or LBBB morphology, capture or fusion beats, etc.

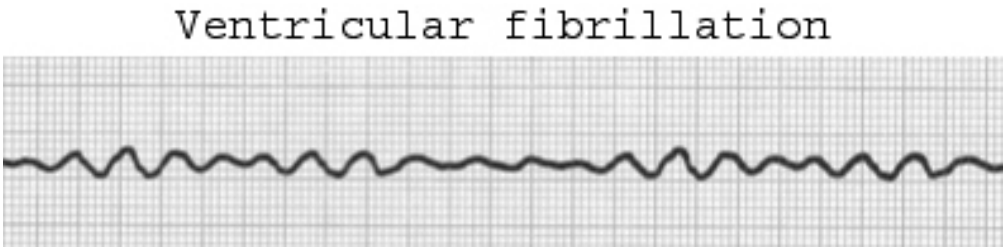
INVESTIGATIONS:

- ECG
- Echocardiography
- Rule out causes ischemia, hyperkalemia, acidosis, etc.

MANAGEMENT:

- Maintain circulation, airway and breathing.
- Resuscitation if needed.
- If hemodynamically unstable then give DC cardioversion with 120 – 200 J shock.
- If hemodynamically stable or if shock refractory then give AMIODARONE 300 mg IV. It may be repeated as a 150 mg dose or may be started as an infusion of 60 mg per hour for 6 hours then 30 mg per hour for 18 hours. It may then be switched to oral suppressive drugs (amiodarone, beta-blockers).
- Other drug options include lidocaine, sotalol and procainamide.
- Electrophysiologic mapping may be done and source ablated in case of recurrent VT.
- If no cause is found then an implantable cardioverter defibrillator (ICD) may be placed.
- In case of Torsades de pointes give MgSO4 2 g IV STAT. Other options include DC cardioversion, isoproterenol infusion or overdrive pacing.
- Correct underlying causes e.g. ischemia, drugs, hyperkalemia, etc.





4.10.10. VENTRICULAR FIBRILLATION (VF)

"It is a chaotic ventricular rhythm with no definite QRS complexes."

TYPES:

- Fine VF: low amplitude waves (<3 mm)
- Coarse VF: waves >3 mm

PRESENTATION:

- Cardiac arrest
- Sudden death

MANAGEMENT:

- Maintain circulation, airway and breathing.
- Start resuscitation.
- Immediate DC cardioversion with 120 – 200 J biphasic shock.
- If shock refractory (3 consecutive shocks fail to revert rhythm) → amiodarone or lidocaine
- Remove precipitating causes e.g. ischemia, hyperkalemia, acidosis.

⇨ ***VF is the most common cause of out-of-hospital cardiac arrest.***
⇨ ***VT and VF are the most dangerous but potentially revertible arrhythmias.***

4.10.11. PULSELESS ELECTRICAL ACTIVITY (PEA) AND ASYSTOLE

- Any organized rhythm (including bradycardias) which fails to produce a palpable pulse is called pulseless electrical activity. Advanced cardiac life support should be instituted and potential precipitating risk factors be reversed. Asystole is an apparent flat line on ECG with no discernible atrial or ventricular activity. Very fine VF may be mistaken as asystole hence doctors should use clinical judgement and check asystole in at least two leads.

⇨ ***Asystole during resuscitation is the rhythm with most dismal prognosis.***

4.11. HYPERTENSION

"Hypertension is defined as a sustained continuous or episodic blood pressure elevation sufficient enough to cause vascular damage (cerebrovascular, cardiovascular, retinal, renal, etc.)."

QUICK FACTS: HYPERTENSION	
Pathology:	**Continuous or episodic blood pressure elevation → risk of vascular damage** **Primary/ essential** **Secondary causes (e.g. hyperthyroidism, renal artery stenosis, hyperaldosteronism, cushing's syndrome, OSAS, etc.)**
Presentation:	**Asymptomatic** **BP ≥130/ 80 mmHg on two occasions** **Acute or chronic target-organ damage: hypertensive retinopathy, cerebrovascular disease, renal failure, heart failure, etc)**
Diagnosis:	**Clinical diagnosis** **FBS, FLPs, CBC, urea, creatinine, electrolytes, TSH, urine D/R, ECG** **Other tests e.g. uric acid, urine ACR, echocardiography, chest x-ray, tests for secondary hypertension**
Treatment:	**Life-style changes: low salt diet, exercise, weight loss, quit smoking** **Calcium channel blockers, ACEI or ARB, thiazide diuretics** **Beta blockers, vasodilators, alpha blockers, centrally acting sympatholytics, renin inhibitors**

- For practical purposes an averageof systolic blood pressure ≥130 mmHg and/or a diastolic blood pressure of ≥80 mmHg on two separate occasions, is defined as hypertension. If ambulatory blood pressure monitoring is used then a 24-hour average systolic blood pressure ≥125 mmHg and/or 24-hour average diastolic blood pressure ≥75 mmHg is diagnostic.

Table 4.30. CAUSES OF SECONDARY HYPERTENSION

Endocrine causes	Hyperthyroidism Hypothyroidism Cushing's syndrome Pheochrmocytoma Hyperparathyroidism Primary hyperaldosteronism Hypercalcemia Acromegaly
Renovascular hypertension	Renal artery stenosis (atherosclerotic) Renal artery stenosis (fibromuscular dysplasia) Renal infarction Renal artery thrombosis
Renal causes	Renal parenchymal disease Renal cysts (including polycystic kidney disease) Renal tumors (including reninomas) Obstructive uropathy
Drugs	NSAIDs, oral contraceptives, anti-depressants, alcoholism, steroids, cocaine, amphetamine, PCP, pseudoephedrine Serotonin syndrome
Mendelian forms of hypertension	Glucocorticoid-remediable hypertension 17α-hydroxylase deficiency 11ß-hydroxsteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome) Gordon syndrome (Pseudohypoaldosteronism type 2) Liddle syndrome
Others	Coarctation of aorta Obstructive sleep apnea syndrome Pre-eclampsia/ eclampsia Polycythemia

TYPES OF HYPERTENSION:

- Primary or essential hypertension (>90%)

- It is the most common cause of hypertension.
- It usually occurs in those aged 25 – 55 years.

- Secondary hypertension:
  - It is hypertension due to identifiable causes (which are usually treatable).
  - Secondary hypertension is suspected if age is <20 years or >50 years or if there is sudden onset of severe refractory hypertension.
    - Refractory/resistant hypertension: hypertension which remains uncontrolled (>140/90 mmHg) despite use of maximum doses of three separate classes of antihypertensives including one diuretic.
- Hypertensive crises (acute rise in BP above 180/120 mm Hg):
  - Hypertensive urgency:
    - It refers to a hypertensive crisis without evidene of end-organ damage.
    - End-organ damage referes to:
      - Seizures, raised intra-cranial pressure (brain)
      - Renal failure (kidney)
      - Heart failure (heart)
      - Papilledema, retinal hemorrhages, exudates (retina)
  - Hypertensive emergency:
    - It refers to a hypertensive crisis with evidene of end-organ damage.
- Malignant hypertension:
  - It refers to marked hypertension (usually above 180/120 mmHg) with neuroretinopathy.
  - Retinal examination shows flame-shaped hemorrhages, cotton wool spots or papilledema.
  - Patients may have encephalopathy, left ventricular failure, micro-angiopathic hemolytic anemia or fibrinoid necrosis with endarteritis.

Table 4.31. JNC VII CLASSIFICATION OF STAGES OF HYPERTENSION (using office BP recordings)

	Systolic BP (mmHg)	Diastolic BP (mmHg
Optimal BP	<120 and	<80
Normal BP	120 – 129 and	80 – 84
High normal BP	130 – 139 and/or	85 – 89
Stage I hypertension	140 – 159 and/or	90 – 99
Stage II hypertension	160 – 179 and/or	100 – 109
Stage III hypertension	≥180 and	≥110
Isolated systolic hypertension	≥140 and	<90
Isolated diastolic hypertension	<140 and	≥90
ACC/AHA 2017 CLASSIFICATION OF STAGES OF HYPERTENSION		
Normal BP	<120	<80
Elevated BP	120 – 129	<80
Stage 1	130 – 139	80 – 89
Stage 2	≥140	≥90

PATHOGENESIS:

- Arterial blood pressure is generated by two major mechanisms:
  - Cardiac output: it depends on stroke volume and heart rate. Stroke volume depends on preload, afterload and myocardial contractility.
  - Peripheral resistance: it depends on vascular structure and vascular function
  - Mechanism of development of essential hypertension is unclear. It involves:
    - Increased salt intake
    - Renal salt retention
    - Sympathetic overactivity (increased cardiac output)
    - Increased peripheral resistance (increased vascular tone and thickening)
    - Activation of renin-angiotensin system
    - Activity of autonomic nervous system (increased epinephrine and norepinephrine)
    - Endothelial dysfunction (imabalance between nitric oxide and endothelin)
    - Genetic factors

Table 4.32. TARGET ORGAN DAMAGES IN HYPERTENSION	
Cardiac	Acute: acute pulmonary edema (hypertensive failure), myocardial infarction Chronic: coronary artery disease, left ventricular hypertrophy, hypertrophic cardiomyopathy, heart failure
Cerebrovascular	Acute: intracerebral hemorrhage, encephalopathy, seizures, TIA, stroke Chronic: TIA, stroke, Charcot-Bouchard aneurysms, dementia
Blood vessels	Aneurysms, aortic dissection, accelerated atherosclerosis
Renal	Acute: hematuria, acute renal injury Chronic: proteinuria, nephrosclerosis, increased risk of FSGS, chronic renal injury
Retinal	Acute: papilledema, hemorrhages Chronic: hypertensive retinopathy

Table 4.33. GRADES OF HYPERTENSIVE RETINOPATHY (KEITH-WAGENER-BARKER CLASSIFICATION)	
GRADE I	Silver wiring of arteries Mild retinal arteriolar narrowing
GRADE II	Grade I + Arteriovenous nipping or nicking Banking sign Salus sign
GRADE III	Grade II + Cotton wool spots Flame-shaped hemorrhages
GRADE IV	Grade III + Papilledema Macular star (ring of exudates around macula)

APPROACH:

- Take complete history.
  - Symptoms: Asymptomatic (mostly); non-specific symptoms include headache, nausea,
  - Duration of hypertension
  - History of other disorders e.g. diabetes, dyslipidemia, stroke, heart disease, renal disease, etc.
  - Use of antihypertensive medicines and side-effects
  - Habits: salt intake, fat intake, high calorie intake, alcoholism, tobacco intake, drug abuse (cocaine, amphetamine), leisure time activities
  - Socioeconomic assessment
  - Adherence to antihypertensive therapy
- Perform physical examination to confirm hypertension.
  - Assess body parameters like weight, BMI, waist circumference
  - Check for postural hypotension
  - Examine cardiovascular system for evidence of
    - Heart failure e.g. displaced apex beat, S3, heave
    - Precordial murmurs
    - Atherosclerotic arterial disease e.g. carotid bruit, renal bruit, weak or absent peripheral pulses
    - Coarctation of aorta e.g. radiofemoral delay, differential hypertrophy of upper body
  - Respiratory system
    - Left ventricular failure e.g. basal crepitations, wheeze
  - Abdomen:
    - Abdominal masses
    - Polycystic kidneys, renal or adrenal masses, abdominal aortic aneurysm, renal bruit
  - Eyes:
    - Fundoscopy for papilledema, hemorrhages, hypertensive retinopathy
  - CNS:
    - Features of stroke or dementia
- Screen for risk factors of cardiovascular diseases.
- Screen for secondary causes of hypertension.

- Drug-resistant/induced hypertension
- Abrupt onset of hypertension
- Onset of hypertension at <30 year
- Exacerbation of previously controlled hypertension
- Disproportionate TOD for degree of hypertension
- Accelerated/malignant hypertension
- Onset of diastolic hypertension in older adults (age ≥65 y)
- Unprovoked or excessive hypokalemia

- Signs of secondary causes include:
  - Hyperthyroidism: weight loss, signs of Graves disease, tachycardia, warm moist hands
  - Hypothyroidism: obesity, coarse facies, croaky voice, dry hands, bradycardia
  - Cushings syndrome: moon face, central obesity, striae, plethora
  - Pheochromocytoma: thin lean anxious patient, features of neurofibromatosis
  - Hyperparathyroidism:
  - Primary hyperaldosteronism:
  - Acromegaly: macroglossia, enlarged acral parts like hands and feet
  - Renal failure: renal frost
  - Polycystic kidney disease:
  - Obstructive uropathy: palpable urinary bladder
  - Coarctation of aorta: murmur of coarctation, differential hypertrophy of upper body, differential clubbing, differential cyanosis, features of Turner syndrome
  - Obstructive sleep apnea syndrome: mallamapti score of airways, obesity,
- Identify complications of hypertensive disease.

INVESTIGATIONS:

- Basic tests: FBS, fasting lipid profile, CBC, basic metabolic panel, TSH, urine D/R, ECG
- Other tests e.g. uric acid, urine albumin-to-creatinine ratio, echocardiography, chest x-ray, tests for secondary hypertension

SCREENING RECOMMENDATIONS:

USPSTF recommends screening as follows:

- Annual screening for those aged ≥40 years and for those who are at increased risk of hypertension
- Every 3 – 5 years for those aged 18 – 39 years

MANAGEMENT:

- Life-style interventions
  - Every hypertensive patient should adopt these interventions.
  - Only life-style modifications can be advised for stage I hypertension.
  - Weight loss (waist circumference <102 cm for men and <88 cm for women)
  - Reduce dietary salt intake
  - Good potassium diet
  - Increased physical activity
  - DASH diet (Dietary Approaches to Stop Hypertension):
    - Low salt intake <2.3 g/day or lower salt intake <1.5 g/day
    - Whole grains, fruits, vegetables and low-fat dairy products
    - Lean meat, poultry and fish
    - Nuts, seeds and legumes
    - Limit fats and oils
  - Quit tobacco and alcoholism
  - Others e.g. probiotics, increased intake of proteins and fibers, fish oil consumption, reduce stress
- Medical treatment
  - Current guidelines recommend a target BP of <130 mmHG systolic and <80 mmHg diastolic.
  - First line antihypertensives include calcium channel blockers, ACE inhibitors, ARBs or thiazide diuretics.
  - Estimate 10-year cardiovascular risk and treat as follows:
    - Normal BP → promote optimal life-style habits and reassess in one year
    - Elevated BP → non-pharmacological therapy and reassess in 3 – 6 months

- Stage I HTN → if no ASCVD or 10-year CVD risk <10% → non-pharmacological therapy and reassess in 3 – 6 months
- Stage I HTN → if ASCVD present or 10-year CVD risk ≥10% → non-pharmacological therapy + anti-hypertensive therapy and reassess in 1 month → if BP goal not met then assess adherence and/or intensify treatment and reassess in 1 month. If BP goal met then reassess in 3 – 6 months.
- Stage II HTN → non-pharmacological therapy + anti-hypertensive therapy and re-assess in 1 month → if BP goal not met then assess adherence and/or intensify treatment and reassess in 1 month. If BP goal met then reassess in 3 – 6 months.

ANTIHYPERTENSIVE DRUGS:

- Calcium channel blockers (dihydropyridines):
  - Mechanism of action: bind to calcium channels and inhibit calcium entry → muscle relaxation → vasodilation → decrease blood pressure
  - Dihydropyridines: AMLODIPINE, ISRADIPINE, NICARDIPINE, NICARDIPINE SR, NIFEDIPINE XR, NISOLDIPINE CR
- Diuretics:
  - Mechanism of action: block sodium reabsorption at different sites → decrease sodium retention and peripheral vascular resistance→ decreased blood pressure
  - Thiazide diuretics: BENDROFLUMETHIAZIDE, HYDROCHLOROTHIAZIDE, CHLORTHALIDONE, INDAPAMIDE
  - Potassium retaining diuretics: AMILORIDE, TRIAMTERENE
  - Aldosterone antagonists: SPIRONOLACTONE, EPLERENONE
  - Loop diuretics: FUROSEMIDE
- ACE inhibitors:
  - Mechanism of action: block conversion of angiotensin I into angiotensin II by angiotensin converting enzyme → vasodilation → decrease in blood pressure
  - Examples include RAMIPRIL, CAPTOPRIL, LISINOPRIL, FOSINOPRIL, ENALAPRIL, TRANDOLAPRIL, PERINDOPRIL, BENAZEPRIL
- Angiotensin II receptor blockers
  - Mechanism of action: block action of angiotensin II on its receptor
  - Examples include CANDESARTAN, IRBESARTAN, LOSARTAN, TELMISARTAN, VALSARTAN, EPROSARTAN
- Calcium channel blockers (non-dihydropyridines):
  - Mechanism of action: bind to calcium channels and inhibit calcium entry → muscle relaxation → vasodilation, decreased myocardial contractility, decrease heart rate → decrease blood pressure
  - Examples: VERAPAMIL R, VERAPAMIL SR, DILTIAZEM R, DILTIAZEM SR
- Renin inhibitors:
  - Mechanism of action: inhibit action of renin
  - Example: ALISKIREN
- Beta-blockers:
  - Mechanism of action: bind to beta-receptors → block action of catecholamines → decrease myocardial contractility and heart rate
  - Non-selective beta-blockers
    - With intrinsic sympathomimetic activity
      - PINDOLOL, CARTEOLOL, PENBUTOLOL, ALPRENOLOL, OXPRENOLOL
    - Without intrinsic sympathomimetic activity
      - NADOLOL, PROPRANOLOL immediate release, PROPRANOLOL sustained release, TIMOLOL, TERTALOLOL
  - ß1-Selective beta-blockers
    - With intrinsic sympathomimetic activity
      - ACEBUTOLOL, CELIPROLOL
    - Without intrinsic sympathomimetic activity

        - ATENOLOL, METOPROLOL TARTARATE immediate release, METOPROLOL SUCCINATE extended release, BISOPROLOL, BETAXOLOL, BEVANTOLOL, NEBIVULOL
    - Beta-blockers with alpha-blocking activity
        - LABETOLOL, CARVEDILOL
- Alpha-blokcers:
    - Mechanism of action: block action of norepinephrine by binding alpha-receptors → vasodilation
    - Selective: PRAZOSIN, DOXAZOSIN, TERAZOSIN
    - Non-selective: PHENOXYBENZAMINE
- Centrally acting sympatholytics
    - Mechanism of action: bind to alpha2-receptors in brain → decrease sympathetic activity → decrease myocardial contractility, heart rate and produce vasodilation
    - Examples include CLONIDINE, METHYLDOPA, RESERPINE, GUANFACINE
- Direct vasodilators
    - Mechanism of action: unclear → vasodilation → decrease blood pressure
    - Examples include HYDRALAZINE, MINOXIDIL

Table 4.34a. DIFFERENT ANTIHYPERTENSIVE AGENTS WITH THEIR DOSES

Calcium channel blockers	**Non-dihydropyridines** VERAPAMIL R: 40 – 160 mg immediate release tablets three times daily VERAPAMIL SR: 120 – 480 mg sustained release tablet once daily DILTIAZEM R tablet: 30 mg four times daily (up to 320 mg per day in divided doses) DILTIAZEM SR capsule: 90 – 540 mg once daily **Dihydropyridines** AMLODIPINE: 2.5 to 10 mg once daily ISRADIPINE: 2.5 mg twice daily (or 5 mg controlled release once daily) NICARDIPINE: 20 – 40 mg three times daily (or 30 – 60 mg sustained release twice daily) NIFEDIPINE: 30 – 90 mg extended release once daily NISOLDIPINE: 8.5 – 34 mg controlled release tablets once daily
Diuretics	**Thiazide diuretics** BENDROFLUMETHIAZIDE: 2.5 – 5 mg once daily HYDROCHLOROTHIAZIDE: 25 – 50 mg once daily CHLORTHALIDONE: 25 – 100 mg once daily INDAPAMIDE: 1.25 mg once daily **Potassium retaining diuretics** AMILORIDE: 5 – 10 mg once daily TRIAMTERENE: 100 mg twice daily **Aldosterone antagonists** SPIRONOLACTONE: 50 – 100 mg once daily or in divided doses EPLERENONE: 50 mg once daily to twice daily **Loop diuretics** FUROSEMIDE: 20 – 40 mg every 6 – 8 hourly (up to a maximum of 600 mg)
ACE inhibitors	RAMIPRIL: 2.5 - 20 mg in one to two divided doses CAPTOPRIL: 25 – 50 mg 2 – 3 times daily (up to maximum dose of 450 mg per day) LISINOPRIL: 5 – 10 mg once daily (up to maximum 80 mg once daily) FOSINOPRIL: 10 – 20 mg once daily (up to 80 mg per day) ENALAPRIL: 5 – 10 mg once daily (up to 40 mg per day in one or two divided doses) TRANDOLAPRIL: 1 – 2 mg once daily (up to 4 mg per day) PERINDOPRIL: 4 – 8 mg per day in one or two divided doses (up to 16 mg per day) BENAZEPRIL: 5 – 10 mg per day (up to 80 mg per day)
ARBs	CANDESARTAN: 8 – 16 mg per day in one or two divided doses (up to 32 mg per day) IRBESARTAN: 150 – 300 mg per day LOSARTAN: 25 – 100 mg per day in one or two divided doses TELMISARTAN: 40 – 80 mg per day VALSARTAN: 40 – 80 mg twice daily (up to 320 mg per day) EPROSARTAN: 400 – 800 mg per day (in one or two divided doses)
Renin inhibitors	ALISKIREN: 150 – 300 mg per day

Table 4.34b. DIFFERENT ANTIHYPERTENSIVE AGENTS WITH THEIR DOSES	
Beta-blockers non-selective	**With intrinsic sympathomimetic activity** PINDOLOL: 5 mg twice daily (up to 60 mg per day) CARTEOLOL: 2.5 mg once daily (up to 10 mg per day) PENBUTOLOL: 20 – 40 mg once daily ALPRENOLOL: 200 – 400 mg per day in divided doses OXPRENOLOL: 80 – 160 mg per day in 2 -3 divided doses (up to 320 mg per day) **Without intrinsic sympathomimetic activity** NADOLOL: 40 – 80 mg per day (up to 320 mg per day) PROPRANOLOL immediate release: 40 mg twice daily (up to 640 mg per day) PROPRANOLOL sustained release: 80 mg once daily (up to 120 mg per day) TIMOLOL: 10 mg twice daily (up to 30 mg twice daily) TERTALOLOL: 10 mg once daily
Beta-blockers (ß1-Selective)	**With intrinsic sympathomimetic activity** ACEBUTOLOL: 400 – 800 mg per day in 1 – 2 divided doses CELIPROLOL: 200 – 400 mg once daily **Without intrinsic sympathomimetic activity** ATENOLOL: 50 – 100 mg per day METOPROLOL TARTARATE immediate release: 100 – 450 mg per day in single or divided doses METOPROLOL SUCCINATE extended release: 25 – 100 mg once daily (up to 400 mg per day) BISOPROLOL: 5 – 20 mg once daily BETAXOLOL: 10 – 40 mg per day BEVANTOLOL: 200 – 400 mg per day in two divided doses NEBIVULOL: 5 – 40 mg once daily
Beta-blockers with alpha-blocking activity	LABETOLOL: 100 mg twice daily (up to 400 mg twice daily) CARVEDILOL: 6.25 mg twice daily (up to 25 mg twice daily)
Alpha blockers	**Selective** PRAZOSIN: 1 mg PO 2 – 3 times up to 6 – 15 mg per day in divided doses. DOXAZOSIN: 1 mg once daily up to 16 mg per day. TERAZOSIN: 1 mg once daily up to 20 mg per day. **Non-selective** PHENOXYBENZAMINE: 10 mg twice daily (up to 40 mg three times daily)
Centrally acting sympatholytics	CLONIDINE: 0.1 mg twice daily (up to 2.4 mg daily) → also available as transdermal patches METHYLDOPA: 250 mg 2 – 3 times daily (up to 3000 mg per day) RESERPINE: 0.1 – 0.5 mg once daily GUANFACINE: 1 – 2 mg once daily
Direct vasodilators	HYDRALAZINE: 10 – 50 mg four times daily MINOXIDIL: 5 – 40 mg once daily in 1 – 2 divided doses

⇨ ***Hypertension is the most common risk factor for stroke, intracerebral hemorrhage and myocardial infarction.***

⇨ ***Hypertension is the most common risk factor related to global mortality.***

4.12. DISEASES OF AORTA

4.12.1. AORTIC ANEURYSM

"It is an abnormal localized or diffuse dilatation of the abdominal or thoracic aorta with a diameter at least 50% greater than the normal size of the aorta."

- **True aneurysm:** Involves all three layers of the aorta (i.e. intima, media and adventitia) and is covered by endothelium. Its shape is fusiform.
- **False aneurysm/ pseudoaneurysm:** Involves only adventitia. Its shape is saccular.

PATHOPHYSIOLOGY:

- The tensile strength and elasticity of any aorta is contributed by medial layer mostly because of elastin and collagen content. Quantity of elastin decreases significantly in the aorta. Disease processes which degrade elastin may further add to the insult.
- According to Laplace's law

$$\textbf{Arterial wall tension} = \textbf{blood pressure} \times \textbf{radius of artery}$$

- Thus both increased blood pressure and increasing diameter of artery can lead to aneurysm formation by increasing wall tension. Eventually wall tension may lead to rupture of wall.

ETIOLOGY:

- Arteriosclerotic (degenerative) disease (elastic fiber fragmentation and cystic medial degeneration)
- Previous aortic dissection
- Inherited connective tissue disorders like Marfans syndrome, Type IV Ehlers Danlos syndrome
- Atherosclerosis
- Infectious causes like mycotic or syphilitic aneurysms
- Arteritis like Giant cell, Takayasu, Kawasaki, Behçet
- Traumatic
- Smoking

⇨ ***The most common site of aneurysm formation is in the infra-renal segment of the abdominal aorta.***

4.12.1.1. THORACIC AORTIC ANEURYSM

"A dilatation of abdominal aorta ≥3 cm in diameter (or ≥50% increase in normal size) is defined as aneurysm."

QUICK FACTS: THORACIC AORTIC ANEURYSM	
Pathology:	**Decrease in elastin quantity in aorta + increase in blood pressure → increased wall tension → dilatation**
Presentation:	**Asymptomatic** **Chest or back pain, features of compression of local structures** **Rupture: pain, hypotension**
Diagnosis:	**Chest x-ray** **Trans-thoracic echocardiography** **CT chest or CT angiography** **Aortography**
Treatment:	**Aneurysm ≥6cm diameter: repair via endovascular grafting or open surgery**

PRESENTATION:

- Asymptomatic (incidentally discovered during chest imaging)
- **Ascending aorta aneurysms:** Chest pain
- **Descending aorta aneurysm:** Back pain or epigastric pain
- **Arch of aorta aneurysm:** Pain in neck
- **Compression/ erosion of tracheobronchial tree:** dyspnea, stridor, wheeze, cough, hemoptysis
- **Compression/ erosion of esophagus:** dysphagia, hematemesis
- **Ruptured aneurysm:** Pain and hypotension
- May present as superior vena cava obstruction, aortic regurgitation, recurrent laryngeal nerve compression, spinal cord compression, spinal artery thrombosis.

INVESTIGATIONS:

- Hemoglobin: for blood loss in case of rupture
- Renal function tests: if also involving abdominal aorta
- Blood group and cross match: for transfusion
- Chest radiograph: may show widened mediastinum or aneurysmal shadow
- Trans-thoracic echocardiography: also helps in identifying aortic regurgitation
- Trans-esophageal echocardiography: accurately differentiates between aneurysm and dissection
- Aortography
- CT scan with contrast
- CT angiography
- MRI and MRA

MANAGEMENT:

- Aneurysm ≥6cm diameter: repair via endovascular grafting or open surgery
- Repair is associated with numerous complications including hemorrhage, paraplegia and stroke.
- General advice: stop smoking, control blood pressure with ACEI or ARBs

4.12.1.2. ABDOMINAL AORTIC ANEURYSM

"A dilatation of abdominal aorta ≥3 cm in diameter (or ≥50% increase in normal size) is defined as aneurysm."

QUICK FACTS: ABDOMINAL AORTIC ANEURYSM	
Pathology:	**Decrease in elastin quantity in aorta + increase in blood pressure → increased wall tension → dilatation**
Presentation:	**Asymptomatic** **Abdominal pain, pulsatile abdominal mass** **Rupture: pain, hypotension, GI bleed** **Vascular/ embolic phenomena**
Diagnosis:	**Ultrasound abdomen** **CT scan or MRI abdomen** **Angiography**
Treatment:	**Aneurysm <3 cm: no follow-up** **Aneurysm 3 – 4 cm: annual ultrasound** **Aneurysm 4 – 5 cm: monthly ultrasound** **Aneurysm >5 cm or growing rate >1 cm per year: open or endovascular repair**

PRESENTATION:

- Asymptomatic (usually discovered incidentally)
- Expanding or large aneurysm: backache, flank pain, groin pain, abdominal pain, pulsatile abdominal mass
- Ruptured aneurysm: severe pain; shock (vitals may not be unstable in case of retroperitoneal rupture); GI bleed (if ruptures into duodenum); congestive heart failure due to AV fistula (if ruptures into vena cava)
- Vascular/ embolic phenomena: livedo reticularis, blue toe syndrome, claudication, impotence

INVESTIGATIONS:

- Ultrasound: standard investigation
- Hemoglobin, PT, APTT, INR, blood group and cross matching
- Abdominal radiograph: not much useful; may show aortic wall calcification
- CT scan or MRI
- Angiography

MANAGEMENT:

- Aneurysm <3 cm: no follow-up needed
- Aneurysm 3 – 4 cm: annual ultrasound for size and rate of expansion
- Aneurysm 4 – 5 cm: 6-monthly ultrasound
- Aneurysm >5 cm (in females >4.5 cm) or growing at a rate of >1 cm per year: repair
- Repair is done by open or endovascular techniques.

⇨ ***Most common site for development of abdominal aortic aneurysm is infra-renal segment.***

4.12.2. AORTIC DISSECTION

"It is a tear in the tunica intima which separates the intima from the aortic wall causing a false lumen."

QUICK FACTS: AORTIC DISSECTION	
Pathology:	**Cystic medial necrosis, atherosclerosis and inflammation of aorta → tear within wall**
Presentation:	**Sudden sharp tearing chest pain, back or abdominal pain** **Hypertension, hypotension, tachycardia, tachypnea** **Complications: AR, CHF, MI, cardiac tamponade, renal failure, mesenteric infarction, paraplegia**
Diagnosis:	**CT scan, MRI or trans-esophageal echo** **Aortogram**
Treatment:	**Type A: surgical or endovascular treatment** **Type B: medical treatment (lower shear wall stress and BP) with beta-blockers (calcium channel blockers if contraindicated), sodium nitroprusside, surgery or endovascular treatment in case of organ failure**

Table 4.35. RISK FACTORS FOR AORTIC DISSECTION

Uncontrolled hypertension (most common)
Increased age
Tobacco use
Dyslipidemia
Cocaine
Connective tissue disorders like Marfan's syndrome or Ehler's-Danlos syndrome
Bicuspid aortic valve
Coarctation of aorta
Vasculitis e.g. Giant cell arteritis, Takayasu arteritis, syphilis, Behçet's disease
Direct trauma
Prior aortic surgery
Pregnancy

Table 4.36. CLASSIFICATION OF AORTIC DISSECTION

STANFORD SYSTEM	DEBAKEY SYSTEM
Type A involves ascending aorta Type B does not involve ascending aorta	Type I starts from ascending aorta and extends distally Type II is confined to ascending aorta Type III starts from descending aorta and extends distally or rarely proximally

TYPES:

- Acute <2 weeks duration
- Chronic >2 weeks duration

PATHOGENESIS:

- Cystic medial necrosis
- Atherosclerosis
- Inflammation of aorta

SYMPTOMS:

- Chest pain (typically sharp sudden tearing or stabbing nature), back pain, abdominal pain
- **If dissection extends to aortic valve:** aortic regurgitation, congestive heart failure
- **If dissection extends to coronaries:** Myocardial infarction
- **If dissection ruptures in pericardial space:** cardiac tamponade
- **If dissection extends to viscera:** mesenteric infarction, renal failure
- **If dissection extends to intercostal arteries:** paraplegia

SIGNS:

- Hypertension, hypotension, tachycardia, tachypnea. Findings related to the extent of dissection.

INVESTIGATIONS:

- 12-lead ECG
- Chest radiograph: May show widened aorta, widened mediastinum, calcium sign
- CT scan, MRI, Trans-esophageal echocardiography: show false lumen and intimal flap
- Aortography

TREATMENT:

- Type A dissections: surgical treatment, endovascular stent-grafting
- Type B dissections: medical treatment
- Goals of medical therapy are to lower shear stress on the aortic wall (dP/dt) and blood pressure. Beta-blockers are the drugs of choice. Calcium channel blockers are used if beta blockers are contra-indicated.
- Beta-blockers (propranolol, esmolol, labetalol) are used to control heart rate <60 and MAP <60-70 mmHg. Sodium nitroprusside is used to lower BP further.
- Avoid agents that increase dP/dt e.g. hydralazine, adrenaline, dopamine.

⇨ ***The most common site of aortic dissection is ascending aorta just above the right or non-coronary sinus.***

⇨ ***Calcium sign: Separation of intimal calcification from outer soft tissue border by at least 1 cm.***

4.13. PERIPHERAL ARTERIAL DISEASE (PAD)

Aka arteriosclerosis obliterans

"It is a disease with reduction in blood flow to tissues other than heart and brain."

QUICK FACTS: PERIPHERAL ARTERIAL DISEASE	
Pathology:	**Atherosclerotic disease → narrowing of lumen → ischemia → may lead to thromboembolism**
Presentation:	**Chronic: intermittent claudication, limb ulcers, limb fatigue, atrophic changes** **Weak pulses** **Acute: impending or overt gangrene**
Diagnosis:	**Ankle-brachial index** **Ultrasound arterial doppler, CTA, MRA or invasive angiography**
Treatment:	**Best medical therapy (quit smoking, control risk factors, weight loss, exercise, anti-platelets, cholesterol lowering agents)** **Phosphodiesterase inhibitors e.g. cilostazol** **Angioplasty/ stenting** **Bypass grafting**

It occurs due to atherosclerosis and is usually associated with coronary artery disease. Lower limbs are more commonly involved.

- Chronic limb ischemia: lasts at least 14 days duration.
- Acute limb ischemia: lasts less than 14 days duration.
- Critical limb ischemia: rest pain and/or tissue loss (ulceration or gangrene) over a period of less than 14 days associated with an ankle BP <50 mmHg.
- Sub-critical limb ischemia: rest pain with an ankle BP >50 mmHg.

PATHOPHYSIOLOGY:

- Focal, multi-focal or diffuse narrowing of artery due to atherosclerosis → ischemia (initially demand-related and when severe becomes rest pain) → may progress to gangrene acutely in case of thrombosis, embolism or trauma

RISK FACTORS:

- Male gender, smoking, diabetes, dyslipidemia, family history

- Buerger's disease (thrombangitis obliterans): is a non-atherosclerotic inflammatory obliterative arterial disease associated with smoking.

PRESENTATION:

- Chronic ischemia: intermittent claudication (exertional pain in muscles, cramping nature), limb ulcers, atrophic changes in limbs, weakness in limbs on walking, limb fatigue, erectile dysunction
- Critical limb ischemia: impending or overt gangrene

INVESTIGATIONS:

- Screening:
  - Pulses examination
  - Ankle-brachial index
    - Normal ABI is >1.0
    - In intermittent claudication it is usually 0.5 – 0.9
    - In critical limb ischemia it is <0.5
- Confirmation:
  - Ankle-brachial index (ABI)
    - Ratio of systolic blood pressure at ankle compared to brachial artery
  - Arterial flow waveforms: prevents false interpretation of ABI. Monophasic flow indicates severe insufficiency.
  - CT angiography, MR angiography, invasive angiography: these tests are usually performed when invasive treatment is desired.

MANAGEMENT:

- Best medical therapy
  - Quit smoking. Nicotine replacement therapy if needed.
  - Risk factor reduction e.g. hypertension, anemia, heart failure
  - Weight loss
  - Consistent, moderate exercise (at least 30 minutes of walking, three times per week)
  - Antiplatelet agents e.g. ASPIRIN or CLOPIDOGREL
  - Cholesterol lowering (low fat diet and statins)
- Phosphodiesterase inhibitors: CILOSTAZOL 100 mg twice daily
- Endovascular techniques: angioplasty and stenting for segmental lesions
- Surgical intervention: bypass grafts

4.13.1. AORTO-ILIAC DISEASE

- Lesions occur in distal aorta, common iliac arteries, external or internal iliac arteries.
- Patients present with intermittent claudication (pain mostly in calf), exertional limb weakness or limb fatigue. Erectile dysfunction may occur in bilateral disease.
- Treatment includes best medical therapy, phosphodiesterase inhibitors, angioplasty or prosthetic aorto-femoral bypass graft.

4.13.2. DISEASE OF SUPERFICIAL AND COMMON FEMORAL ARTERIES

- Lesions occur in superficial femoral artery (most common), common femoral and popliteal arteries.
- Patients present with claudication pain confined to calf.
- Dependant redness of feet may be seen in severe cases which will blanch on elevation. Lower legs and feet may show shiny atrophic skin, hair loss and disuse atrophy of muscles.
- Conservative management is usually sufficient. In case of progressive severe disease, femoral-popliteal bypass or sndovascular stenting may be performed. Thromboendarterectomy may be done in selected lesions.

4.13.3. DISEASE OF LOWER LEG AND FOOT ARTERIES

- Claudication may not be evident due to collateral blood supply. If it occurs, there is severe burning pain on dorsum of foot that is relieved with dependency. Severe disease may manifest as rest pain,

skin changes or ulceration. Dependant rubor may be present with blanching on elevation. ABI is ≤0.3 and waveform analysis may show monophasic flow. Aside from conservative treatment, bypass grafting is the primary method of revascularization. Gangrene may require amputation.

4.13.4. ACUTE LIMB ISCHEMIA

- There is acute occlusion of an artery predisposing to gangrene.
- It is caused by thrombosis of a pre-existing arterial lesion, embolization from a lesion or embolization from heart (e.g. atrial fibrillation, mitral stenosis, mural thrombi).
- Patients may develop pain, pallor, pulselessness and cold periphery. Paresthesia and paralysis of limb indicate irreversible ischemia. Immediate revascularization is needed while keeping the patients anticoagulated. Options include catheter directed chemical or mechanical thrombolysis or surgical intervention.

4.14. PULMONARY HYPERTENSION

"It is a condition resulting from any of a group of disorders which is characterized by a mean pulmonary arterial pressure of 25 mmHg or greater at rest during right heart catheterization."

QUICK FACTS: PULMONARY HYPERTENSION	
Pathology:	**Increased pulmonary vascular resistance → increased RV systolic pressure → eventual RV failure**
Presentation:	**Exertional dyspnea, fatigue, angina, near-syncope, syncope** **Signs of pulmonary hypertension** **Signs of right heart failure** **Features of underlying diseases**
Diagnosis:	**Echocardiogram** **Cardiac catheterization with vasodilator testing** **Chest x-ray, HRCT or workup for underlying cause**
Treatment:	**Vasoreactive: calcium channel blockers** **Non-reactive: endothelin antagonists, PDE-V inhibitors, prostacyclins** **Lung transplantation** **Anti-coagulation (severe)**

Table 4.37. HEMODYNAMIC TYPES OF PULMONARY HYPERTENSION

Pre-capillary pulmonary hypertension	PAP≥25 mmHg PAWP≤15 mmHg	Pulmonary arterial hypertension Pulmonary hypertension due to lung diseases Chronic thromboembolic pulmonary hypertension Pulmonary hypertension with unclear and/or multifactorial mechanisms
Post-capillary pulmonary hypertension	PAP≥25 mmHg PAWP>15 mmHg	Pulmonary hypertension due to left heart diseases Pulmonary hypertension with unclear and/or multifactorial mechanisms
Isolated post-capillary pulmonary hypertension	DPG <7 mmHg and/or PVR ≤3 Wood units	
Combined post-capillary and pre-capillary pulmonary hypertension	DPG ≥7 mmHg and/or PVR >3 Wood units	

- Pulmonary hypertension is also said to be present if mean pulmonary artery pressure is >30 mmHg during exercise.
- Normal mean pulmonary artery pressure is 14±3 mmHg (maximum up to 20 mmHg).
- **Idiopathic pulmonary arterial hypertension** (aka primary pulmonary hypertension) is an uncommon condition mostly presenting in females in their fourth and fifth decades. In some case it is associated with type II bone morphogenetic protein mutations.

PATHOPHYSIOLOGY:

- Increase in pulmaonary vascular resistance → increase in RV systolic pressure → increased RV workload and oxygen demand → RV failure

SYMPTOMS:

- Exertional dyspnea, fatigue, angina, near-syncope, syncope, peripheral edema

SIGNS:

- Palpable second heart sound, loud P2, RV third or fourth sound, increased JVP, tricuspid regurgitation, reduced carotid pulse, right ventricular heave
- Signs of congestion: hepatomegaly, ascites, peripheral edema
- Signs of underlying disease e.g. signs of interstitial lung disease, scleroderma, CLD.

Table 4.38. WHO CLASSIFICATION OF PULMONARY HYPERTENSION	
Pulmonary arterial hypertension	Idiopathic Hereditary – BMPR2 mutations and other mutations Drugs and toxin induced Associated with other disorders – connective tissue disorders, HIV, portal hypertension, congenital heart disease, schistosomiasis
	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
	Persistent ppulmonary hypertension of the newborn
Pulmonary hypertension due to left heart disease	Left ventricular systolic dysfunction Left ventricular diastolic dysfunction Valvular disease
Pulmonary hypertension due to lung disease/ hypoxia	Obstructive and restrictive lung diseases Sleep-disordered breathing Alveolar hypoventilation disorders
Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstruction	Chronic thromboembolic pulmonary hypertension Other pulmonary artery obstructions e.g. angiosarcoma, parasites, arteritis
Pulmonary hypertension with unclear and/or multifactorial mechanisms	Hematological disorders e.g. hemolytic anemia, myeloproliferative disorders Systemic disorders e.g. sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis Metabolic disorders e.g. glycogen storage disease, gaucher disease Others

Table 4.39. WHO FUNCTIONAL FUNCTIONAL CLASSIFICATION OF OF PULMONARY HYPERTENSION	
I	Pulmonary hypertension without limitation of physical activity. Ordinary physical activity does not cause symptoms.
II	Pulmonary hypertension with slight limitation of physical activity. Patietns are comfortable at rest however ordinary physical activity causes symptoms.
III	Pulmonary hypertension with marked limitation of physical activity. Patients are comfortable at rest however less than ordinary activity causes symptoms.
IV	Pulmonary hypertension with inability to carry out any physical activity without symptoms. Signs of right heart failure are present. Symptoms may be present at rest.

INVESTIGATIONS:

- Chest x-ray: may show enlarged pulmonary arteries or lung pathology
- Electrocardiography: may show right axis deviation , right ventricular hypertrophy, right atrial enlargement, right bundle branch block
- Echocardiography: may show enlarged RV and RA, reduced LV and tricuspid regurgitation, abnormal movement of IV septum
- Pulmonary function tests and DLCO
- Cardiac catheterization with vasodilator testing
- High resolution CT scan
- Others e.g. CBC, LFTs, ANA, TSH, LFTs, HIV serology

MANAGEMENT:

- General advice:
    - Encourage patients to remain physically active within physical limits.
    - Advice patients to monitor saturation with pulse oximetry.
    - Stop smoking
    - Low salt intake
- Diuretics to relieve peripheral edema and RV load.
- For pulmonary arterial hypertension
    - Calcium channel blockers in vasoreactive patients e.g. NIFEDIPINE, AMLODIPINE

- Other thearpies are given to non-reactive patients.
  - Endothelin receptor antagonists e.g. BOSENTAN, AMBRISENTAN
  - Phosphodiesterase-V inhibitors e.g. SILDENAFIL, TADALAFIL
  - Prostacyclins for vasodilation e.g. ILOPROST, EPOPROSTENOL, TREPROSTINIL
  - Lung transplantation in severe cases
- Continuous long-term oxygen therapy in patients paO2 <60 mmHg
- Oral anticoagulation in severe pulmonary hypertension

- For other causes treat underlying e.g. thromboendarterectomy and life-long anticoagulation in CTEPH

⇨ ***Most common cause of cor pulmonale is COPD.***

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)

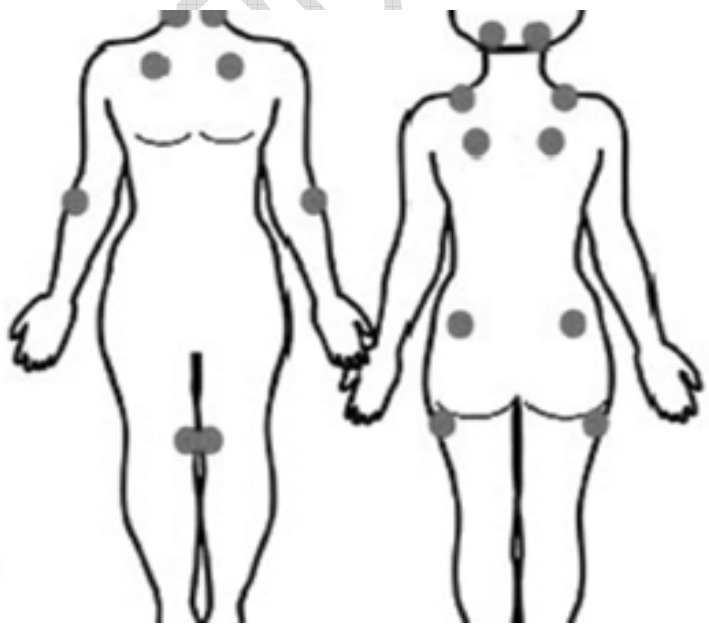
⇨ ***Angioedema without urticaria usually suggests ACEI/ ARB induced angioedema, hereditary angioedema (hereditary C1 INH deficiency) or acquired C1 INH deficiency.***

⇨ ***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**
	Asymptomatic
Presentation:	**Thrombotic complications**
	Complications in pregnancy
	Thrombocytopenia, prolonged APTT
Diagnosis:	**Anticardiolipin antibodies, anti-beta2-glycoprotein antbodies, antiprothrombin antibodies**
	Positive RPR and VDRL
	Non-pregnant: life-long anticoagulation
Treatment:	**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 painful 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** **Red, swollen and painful cartilage → deformities**
Presentation:	**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, 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
- 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.

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)."

PATHOPHYSIOLOGY:

Infection with associated organism→Bacterial lipopolysaccharides and nucleic acids are presented to HLA-B27 →aberrant auto-immune response

Table 9.26: CAUSATIVE ORGANISMS OF REACTIVE ARTHRITIS

- Salmonella enteritidis
- Shigella flexneri
- Shigella disenteriae
- Campylobacter jejuni
- Yersinia enterocolitica
- Clostridium difficile
- Neisseria gonorrhea
- Mycoplasma hominis
- Chlamydia trachomatis
- Human immunodeficiency virus

PRESENTATION:

1 -4 weeks after gastrointestinal or genitourinary infection:

- Acute migratory asymmetric inflammatory oligoarthritis. (usually lower limbs and 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

QUICK FACTS: REACTIVE ARTHRITIS
Reactive arthritis 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.**

EPIDEMIOLOGY:

- Male:Female ratio = 1:1
- Age: 20 – 50 years
- HLA-B27 positive patients (85%)

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
  - Steroids (if uveitis)
- If does not respond then second-line:
  - Steroids (systemic or intra-articular)
  - 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

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** **Response to steroid trial**
Treatment:	**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** **Stages of asthma, eosinophilia and vasculitis**
Presentation:	**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**

Diagnosis:	**Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular rash)** **Arthralgias and arthritis** **Venous and arterial thromboses** **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** **Mostly occurs in proximal end of femur**
Presentation:	**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.***

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:	**Features of anemia**
Presentation:	**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 or β)."

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

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**

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

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

$$\textbf{\textit{Transferrin saturation}} = \frac{\textbf{\textit{Serum iron}}}{\textbf{\textit{TIBC}}} \times 100$$

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**
Treatment:	**Workup for cause: antibodies against intrinsic factor, Schilling test** **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-$ß^0$ thalassemia or sickle-$ß^+$ 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:	**Osmotic fragility test**
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
- Reticulocytes: increased
- Peripheral smear: spherocytes
- Osmotic fragility test: spherocytesswell and rupture easily in hypotonic solutions
- Direct antiglobulin test: negative

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:	**Anemia** **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 37°C	Bind to RBC membranes at 0°C - 5°C
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
    - IMATINIB 400 – 600 mg per day
    - DASATINIB, NILOTINIB, SUNITINIB
- 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.
- 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**
Diagnosis:	**Macroytic anemia without megaloblasts, mild thrombocytopenia, neutropenia** **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**
Diagnosis:	**Absence of lytic lesions, renal involvement or hypercalcemia** **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** **Asymptomatic**
Presentation:	**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** **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
- 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